# Immuno-oncology:

# New possibilities in the fight against cancer

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1

## Disclosures

**Part of the speakers's bureau at Merck Sharp Dohme, Pfizer and Abbvie**

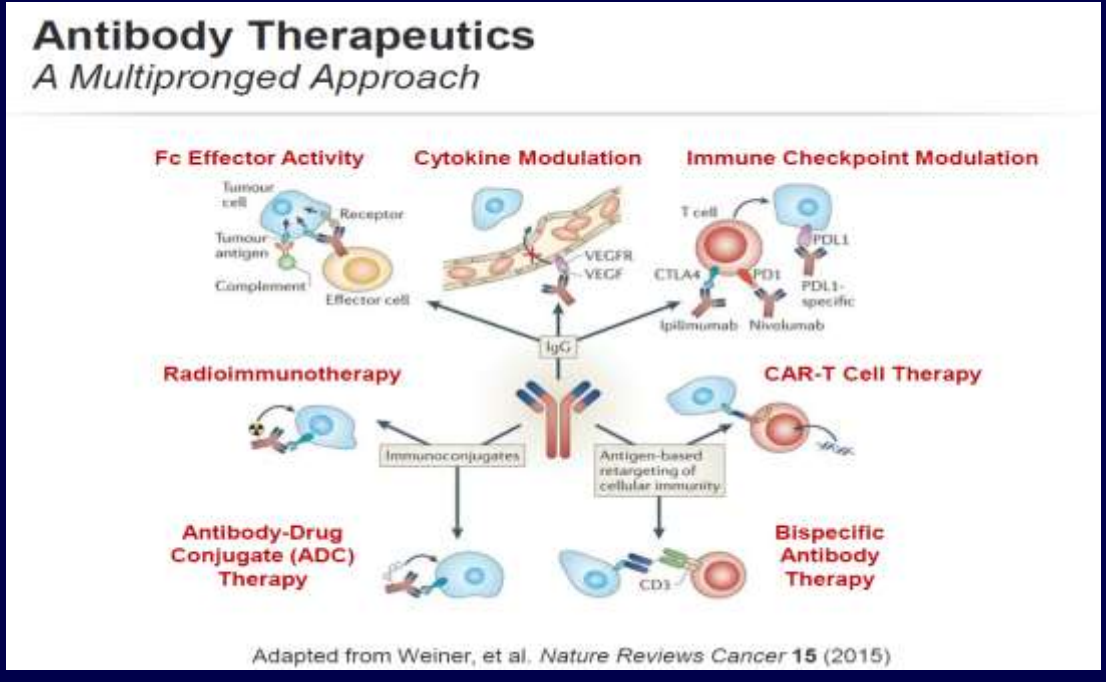
I have divested from relationship with these companies

# Quizz Questions

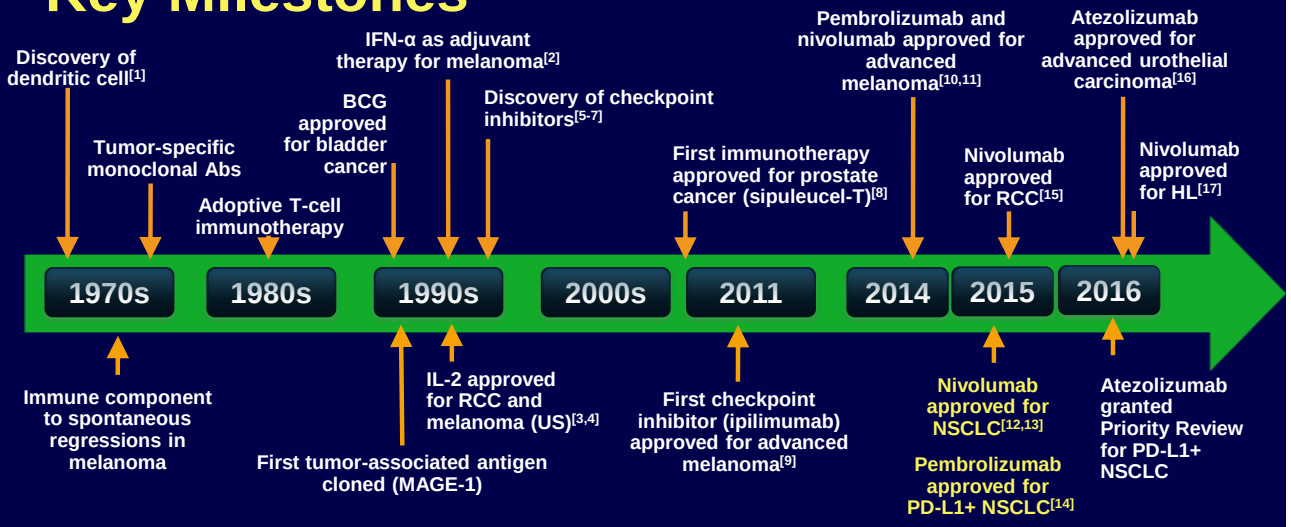
1) Immunotherapy aims to boost immune activation against tumors by inhibition of anergic signals driven by CTLA-4 and PD-L1?

2) Expression of PD-L1 in immune cells is predictive of response to inhibitors of immune-checkpoints?

3) Adverse events to immunomodulator antibodies result from immune-mediated reactions and appear in the first two weeks of treatment?

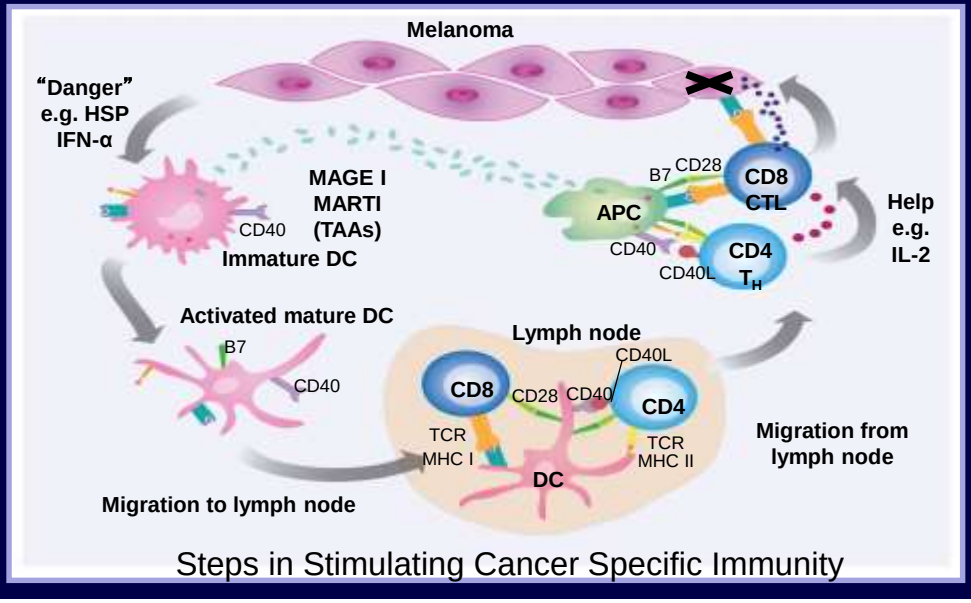


# History of Cancer Immunotherapy: Key Milestones



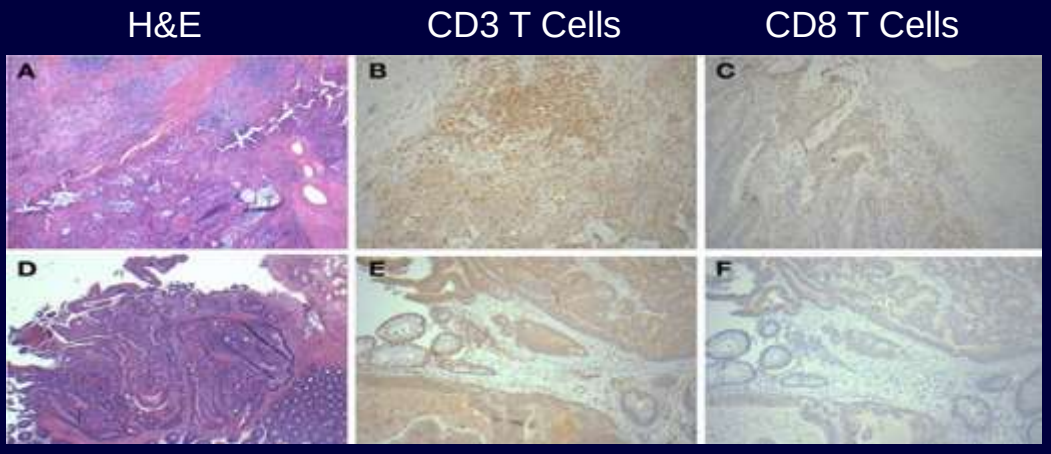

Slide credit: clinicaloptions.com

# Immunogenic cancers are a focus in cancer immunotherapy research




Steps in Stimulating Cancer Specific Immunity

# Genomic Signature Links to T Cell Infiltrates in Tumors




Madhavan S, et al. Front Genetics. 2013;4:236.

# Interferon alfa and Immune cell activation

- Promotes activity of B cells, T cells, macrophages, and dendritic cells
- Increases expression of Fc receptors
- Approved for treatment of cancer for more than 10 years
- Currently indicated for malignant melanoma, follicular lymphoma, hairy-cell leukemia, Philadelphia-positive chronic myeloid leukemia, condylomata acuminata, AIDS-related Kaposi's sarcoma
- Intolerable for some patients because of significant adverse effects

Kirkwood JM, et al. J Clin Oncol. 2000;18:2444-2458.

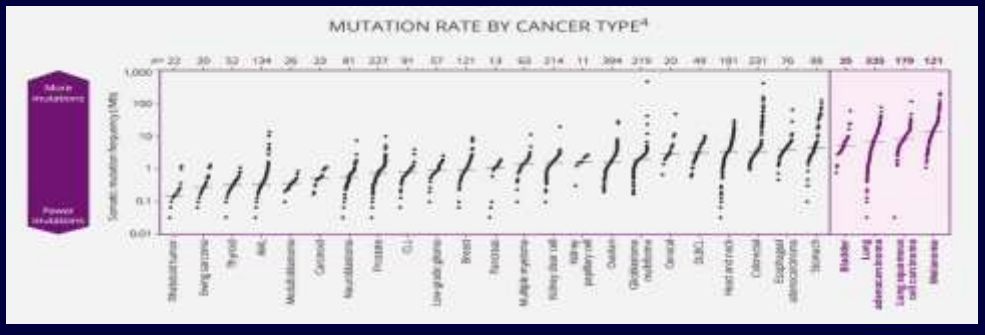
# Interleukin-2 and T-cell activation

- IL-2
  - T-cell growth factor
  - Currently indicated for RCC malignant melanoma
  - Not very robust at inducing tumor responses, but effective at maintaining responses
  - Produces significant adverse effects, including capillary leak syndrome, hypotension, and mental status changes

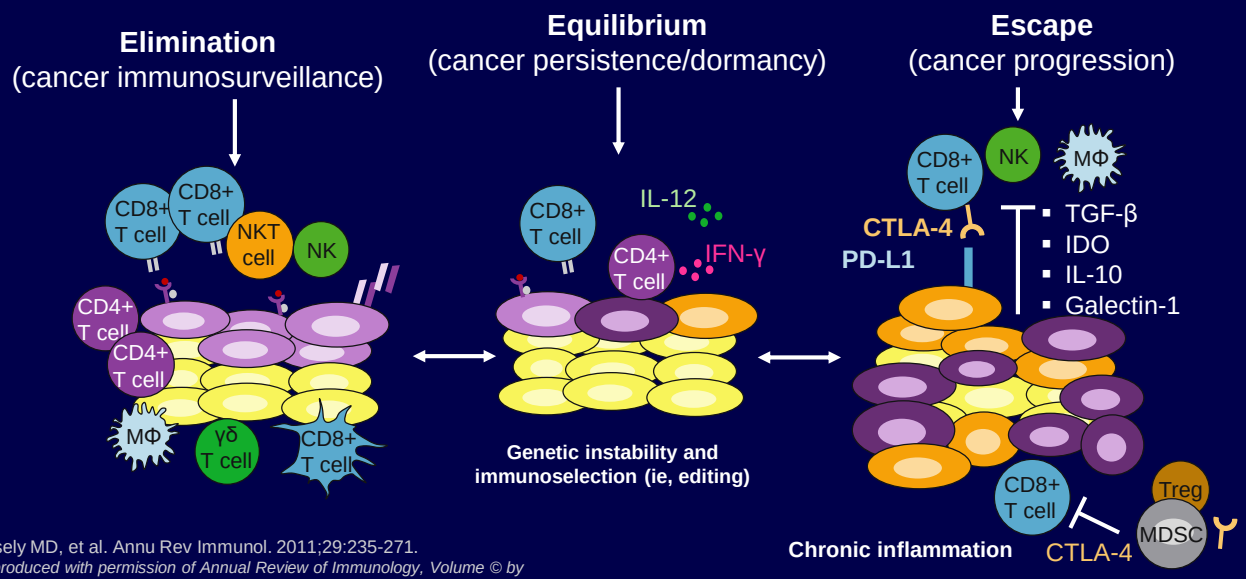
McDermott DF, et al. J Clin Oncol. 2005;23:133-141.

# If the Immune System Is so Potent, Why Do People Get Cancer?

- Cancers look like "self"
  - Cancers are shaped by the host microenvironment.
- Tumors actively defeat the host immune response.



# Multiple Mechanisms of Immune Escape




Vesely MD, et al. Annu Rev Immunol. 2011;29:235-271.
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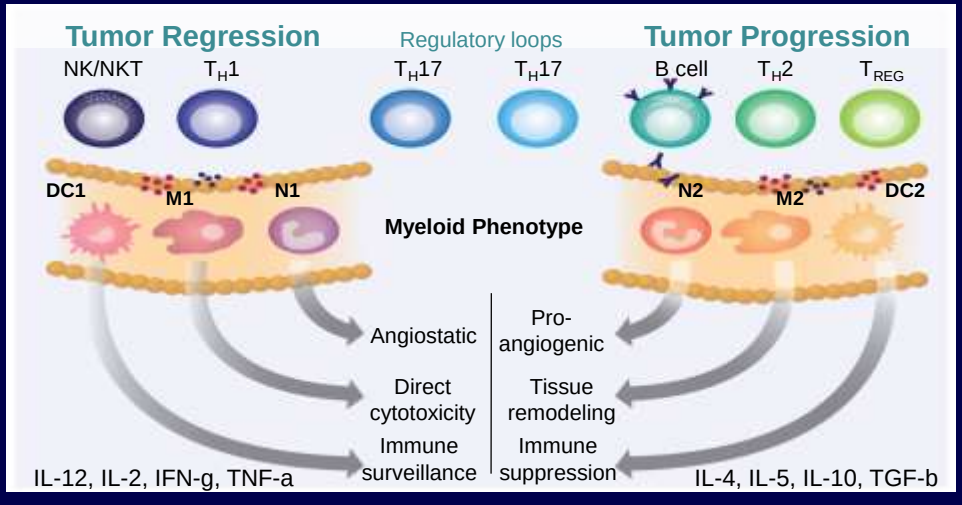
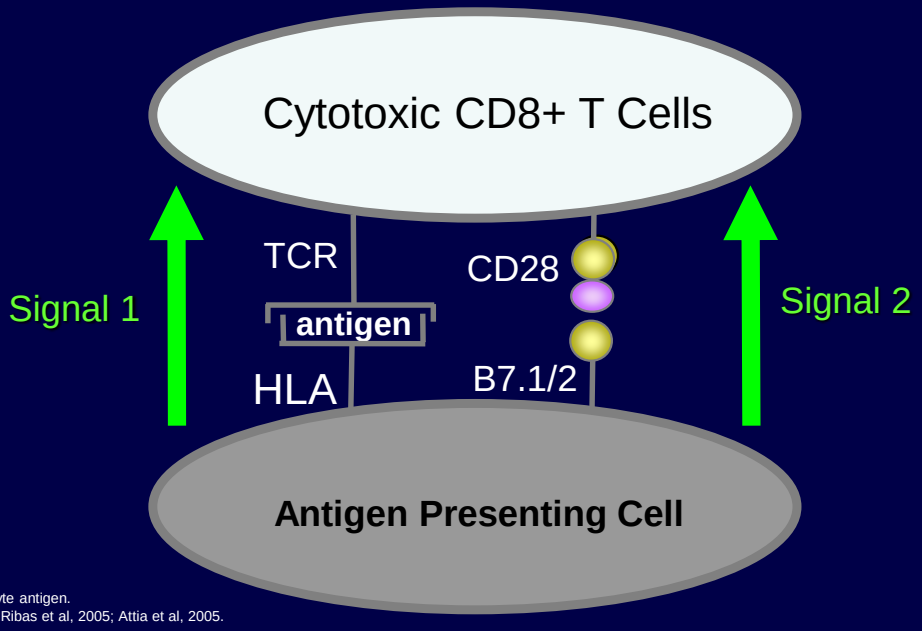
# The Immune System Is All About "Checks and Balances"



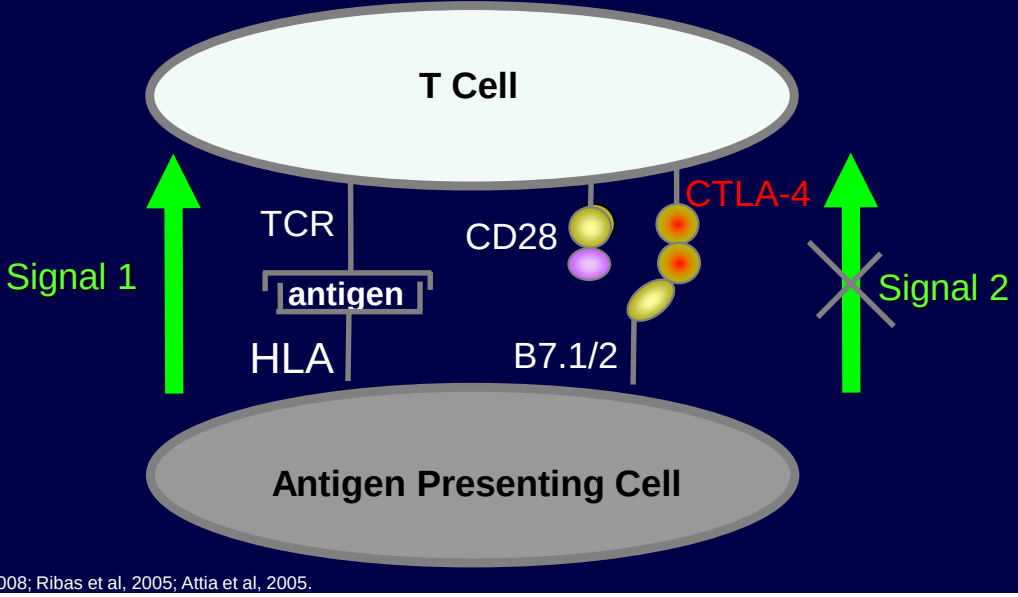

IL = Interleukin; TNF = tumor necrosis factor; TGF = transforming growth factor.
DeNardo et al, 2010.

# Normal T-Cell Activation




HLA = human leukocyte antigen.
Kirkwood et al, 2008; Ribas et al, 2005; Attia et al, 2005.

# Immune Checkpoints (CTLA-4) Prevent Normal T-Cell Activation



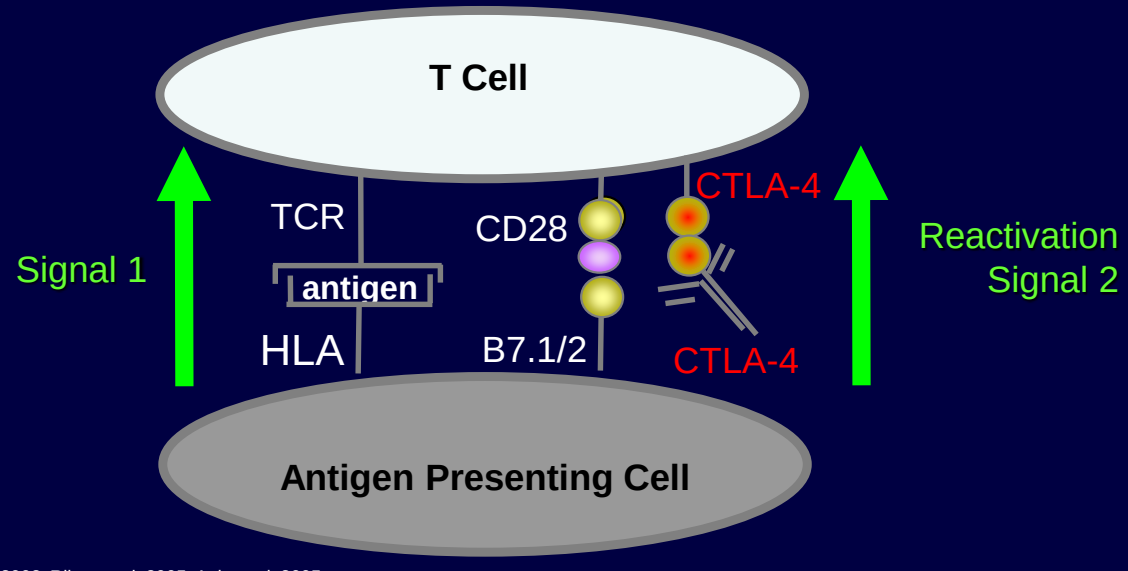

Kirkwood et al, 2008; Ribas et al, 2005; Attia et al, 2005.

# Tumor-Derived Immune Suppression

- Systematic studies have identified multiple mechanisms cancers employ to defeat the immune response
- Goal: therapy strategies that "**liberate**" underlying anticancer immune responses
- Immune checkpoints not even in the picture in 2008!

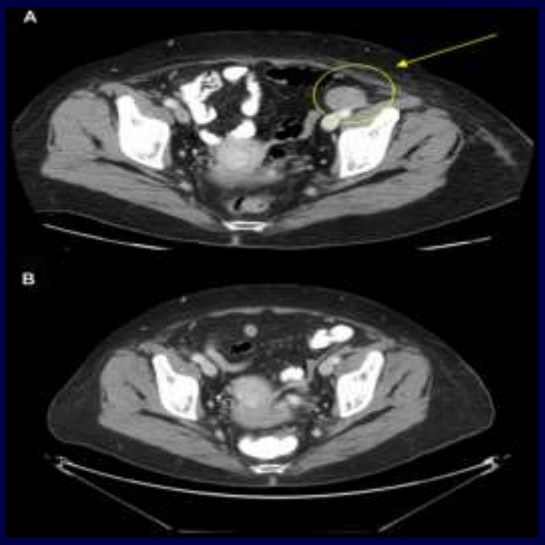
Weiner LM. N Engl J Med. 2008;358:2664-2665.

# Ipilimumab (Anti-CTLA-4) Blocks the CTLA-4 Checkpoint, Restoring T-Cell Activation




Kirkwood et al, 2008; Ribas et al, 2005; Attia et al, 2005.

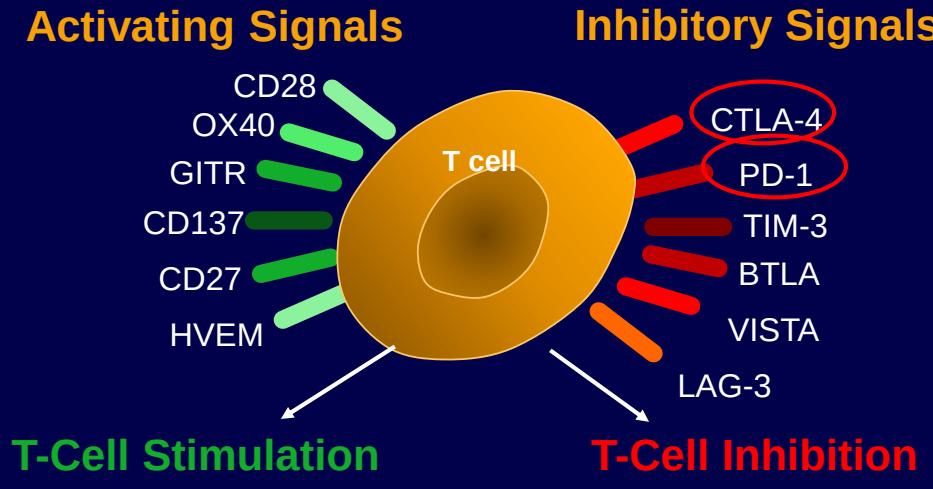
# CTLA-4 Blockade and sustained T-cell activation
## (Ipilimumab, Tremelimumab)




- Single-agent activity
  - RR = 15%–20%
- Regressions = durable
- Regressions = delayed
- Grade III/IV SAE = 10%–15%
  - Colitis
  - Hypophysitis

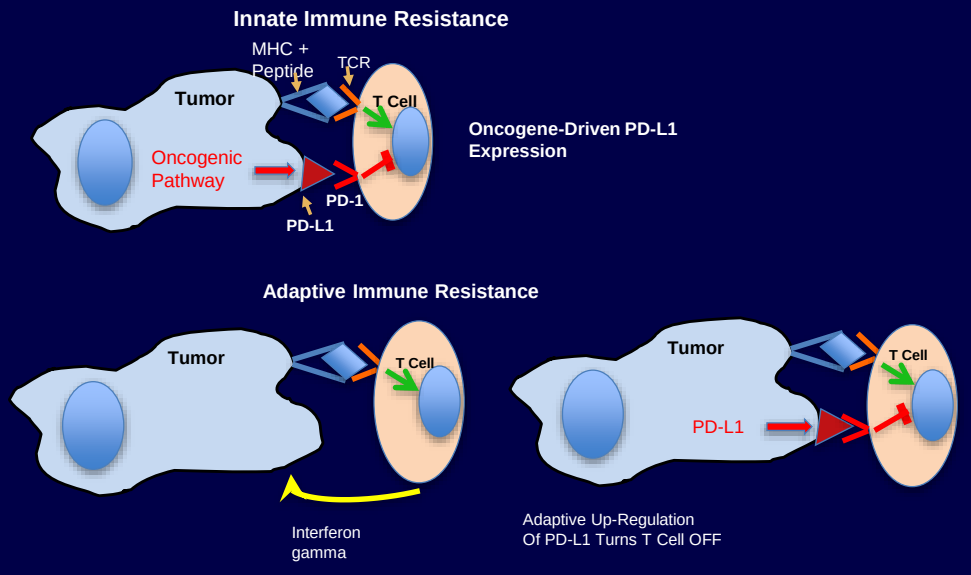
RR = response rate; SAE = serious adverse event; PSA = prostate-specific antigen; PC = prostate cancer.
Saenger et al, 2008; courtesy of Jedd D. Wolchok, MD, PhD.

# T-Cell Response: Accelerate or Brake?



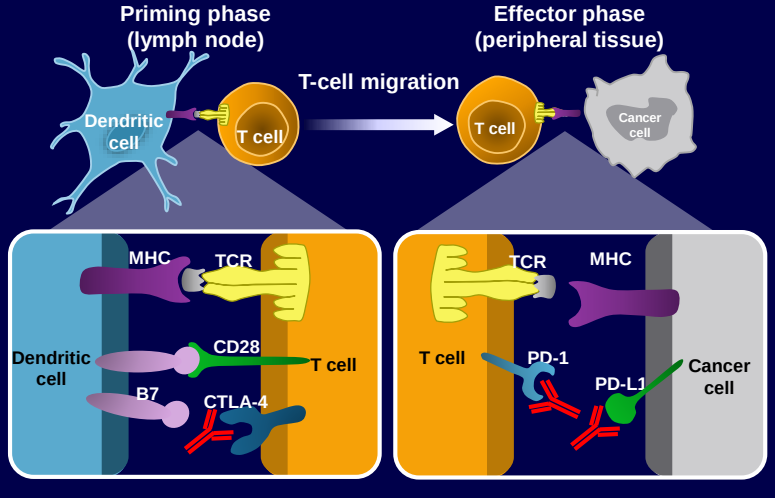

Mellman I, et al. Nature. 2011;480:480-489.

# Immune Resistance: PD-1



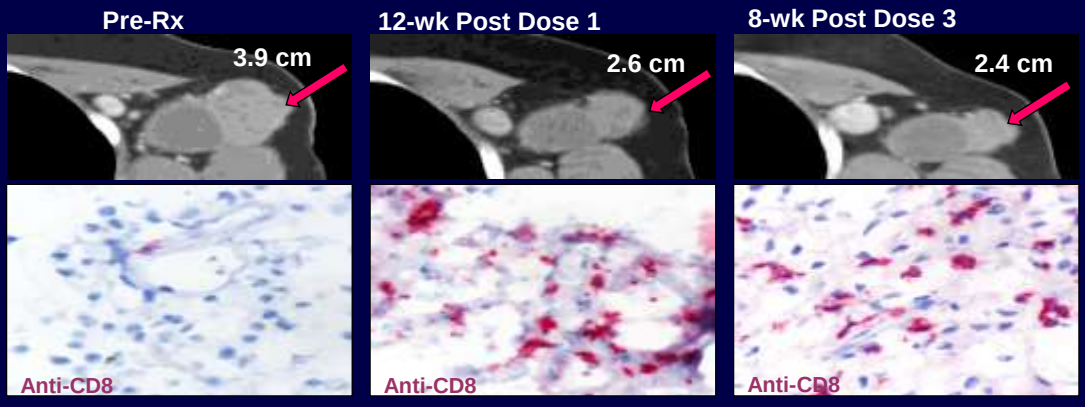

Pardoll, 2012a.

# CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment




Ribas A. N Engl J Med. 2012;366:2517-2519.

# PD-1 Blockade: Results in Increased CD8 T Cells in Tumors




Rx = treatment.
Brahmer et al, 2010.

# Clinical Development of PD-1/PD-L1 Immune Checkpoint Inhibitors

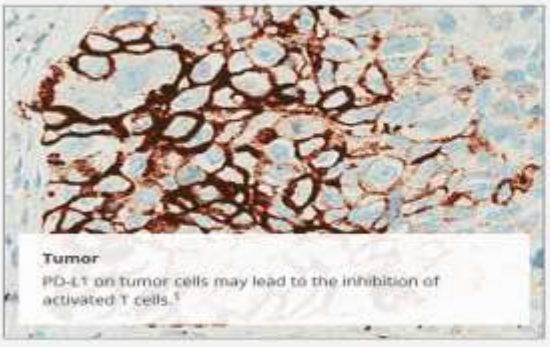
| Target | Antibody | Molecule | Approval/Development Stage |
|---|---|---|---|
| PD-1 | Nivolumab | Fully human IgG4 | Phase I/II/III multiple tumors **Approved: melanoma, NSCLC, RCC, cHL** **Breakthrough Therapy: HNSCC** |
| | Pembrolizumab | Fully human IgG4 | Phase I/II/III multiple tumors **Approved: NSCLC/melanoma** **Breakthrough Therapy: cHL/mCRC** |
| | Pidilizumab (CT-011) | Humanized IgG1 | Phase I/II multiple tumors |

ClinicalTrials.gov.

# PD-1 and PD-L1 as biomarkers for cancer therapy

TUMOR CELLS AND TUMOR-INFILTRATING IMMUNE CELLS BOTH EXPRESS PD-L1[1,2]

**PD-L1 expression detected in immunohistochemistry staining of lung cancer tumor[3]**

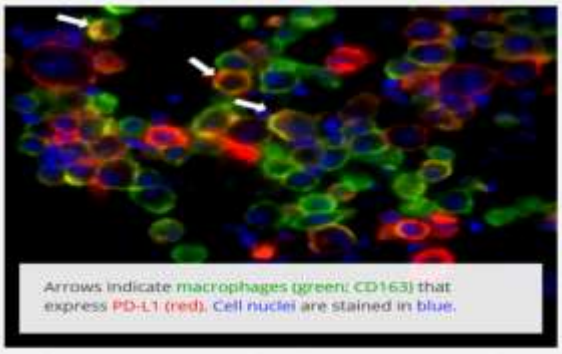


**Tumor**
PD-L1 on tumor cells may lead to the inhibition of activated T cells.[1]

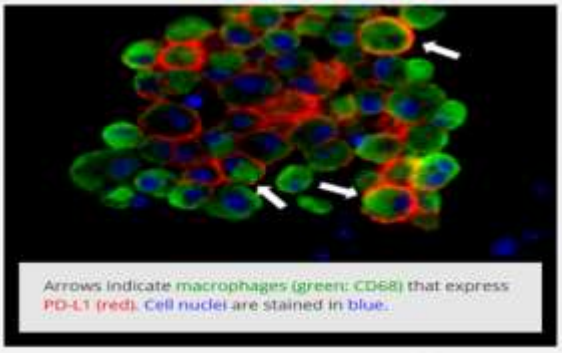
**Tumor-infiltrating immune cell**
PD-L1 on tumor-infiltrating immune cells may also lead to the inhibition of activated T cells.[1,4]

# PD-L1 Expression on Tumor-Inflitrating Immune Cells

**PD-L1 expression on macrophages detected in immunofluorescence staining of lung cancer tumor[3]**



Arrows indicate macrophages (green; CD163) that express PD-L1 (red). Cell nuclei are stained in blue.



Arrows indicate macrophages (green; CD68) that express PD-L1 (red). Cell nuclei are stained in blue.

# PD-L1 expression by cancer type

| CANCER TYPE | PERCENTAGE POSITIVE FOR PD-L1 EXPRESSION[1*] | PRESENCE OF TUMOR-INFILTRATING IMMUNE CELLS[2-21†] |
|---|---|---|
| Melanoma | 40%–100% | ✓[7,8] |
| Non-small cell lung cancer | 35%–95% | ✓[9] |
| Nasopharyngeal | 68%–100% | ✓[10] |
| Glioblastoma/mixed glioma | 100% | ✓[11] |
| Colon adenocarcinoma | 53% | ✓[12] |
| Hepatocellular carcinoma | 45%–93% | ✓[13] |
| Urothelial/bladder | 28%–100% | ✓[14] |
| Multiple myeloma | 93% | ✓[15] |
| Ovarian | 33%–80% | ✓[16] |
| Gastric carcinoma | 42% | ✓[17] |
| Esophageal | 42% | ✓[18] |
| Pancreatic | 39% | ✓[19] |
| Renal cell carcinoma | 15%–24% | ✓[20] |
| Breast | 31%–34% | ✓[19] |
| Lymphomas | 17%–94%[‡] | ✓[21] |
| Leukemias | 11%–42% | – |

# Phase II IMvigor210 at ASCO 2016: Atezolizumab in Urothelial Carcinoma

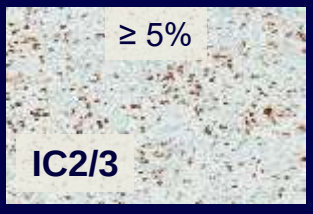
- 2-cohort study in metastatic or locally advanced urothelial carcinoma
- *Cohort 1*: no chemotherapy for metastatic disease[1]
- *Cohort 2*: prior platinum-based chemotherapy (N = 310)[2-4]

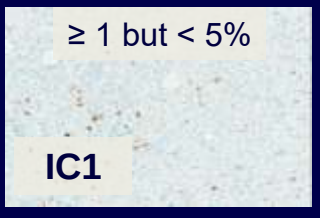
**Atezolizumab FDA approved in May 2016 for the treatment of locally advanced or metastatic urothelial carcinoma with progression during or following platinum chemotherapy**

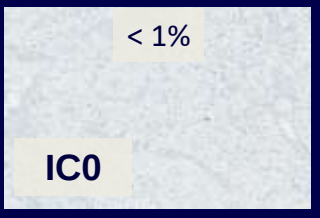
1. Balar AV, et al. ASCO 2016. Abstract LBA4500.
2. Dreicer R, et al. ASCO 2016. Abstract 4515.
3. Rosenberg JE, et al. Lancet. 2016;[Epub ahead of print].
4. Rosenberg JE, et al. ASCO 2016. Abstract 104.

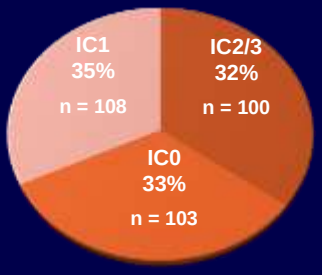
# PD-L1 Expression on Immune Cells: Predictive Marker for Response to Atezolizumab

**IHC Status of Treated Pts in IMvigor210 Study (N = 311)**



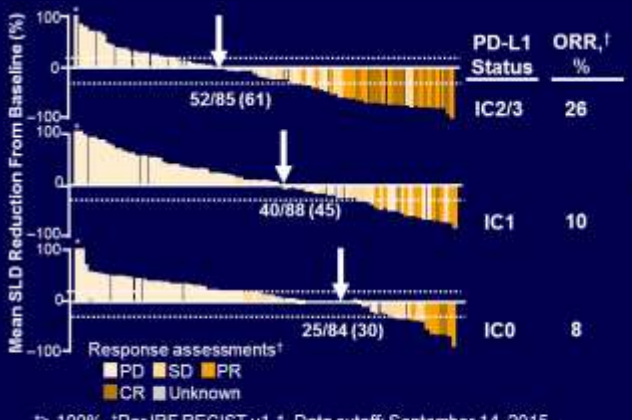




- PD-L1 staining on tumor cells and ICs hypothesized to be biomarker for activity of PD-1/PD-L1 therapy
- Atezolizumab phase II trial: pts enrolled with any PD-L1 status
- PD-L1 expression measured prospectively using companion diagnostic

Rosenberg J, et al. European Cancer Congress 2015. Abstract 21LBA.

# IMvigor210: Change in Tumor Burden by PD-L1 Subgroup



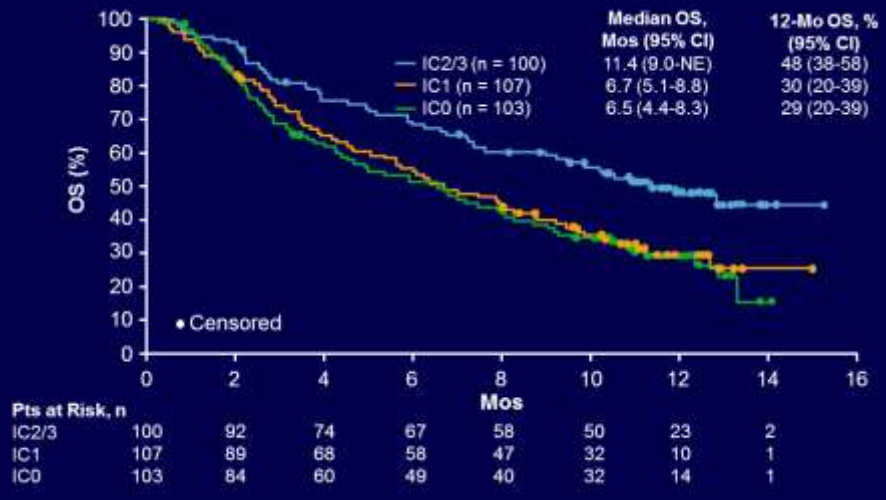

- Reduction in tumor burden associated with PD-L1 status
- 117/257 pts with tumor assessments (46%) had SLD reductions

*> 100%. †Per IRF RECIST v1.1. Data cutoff: September 14, 2015.

Pts without postbaseline tumor assessments included those who discontinued before the first tumor assessment and are not plotted. Several pts with CR had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

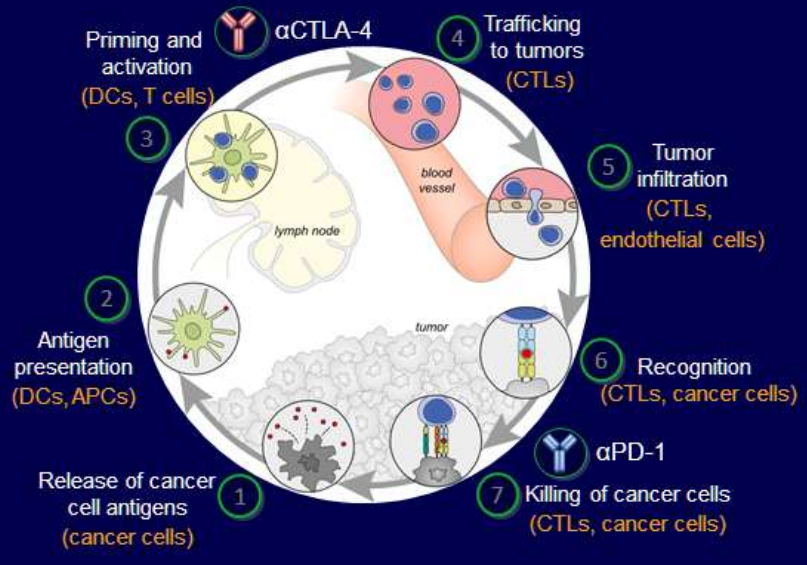
Hoffman-Censits JH, et al. ASCO GU 2016. Abstract 355.

# IMvigor210: OS Associated With PD-L1 Expression on Immune Cells



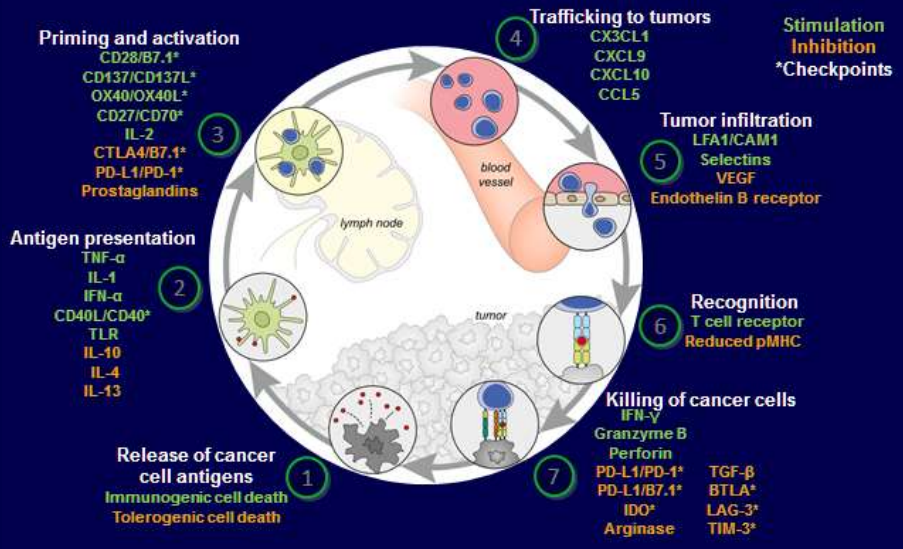

Rosenberg JE, et al. Lancet. 2016;387:1909-1920.

# The Cancer Immunity Cycle




Reprinted from Immunity 39(1). Chen DS, et al. Oncology meets immunology: the cancer-immunity cycle. p. 1-10. Copyright 2013, with permission from Elsevier.

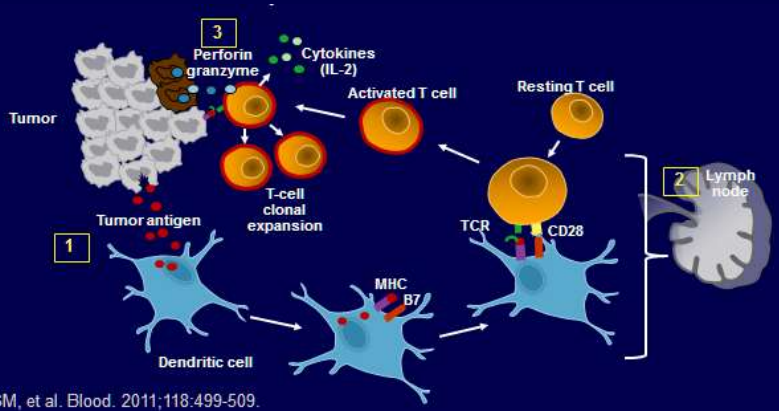
# The Cancer Immunity Cycle




Reprinted from Immunity 39(1). Chen DS, et al. Oncology meets immunology: the cancer-immunity cycle. p. 1-10. Copyright 2013, with permission from Elsevier.

# Immune-Related AEs due to total envolvement of immune system

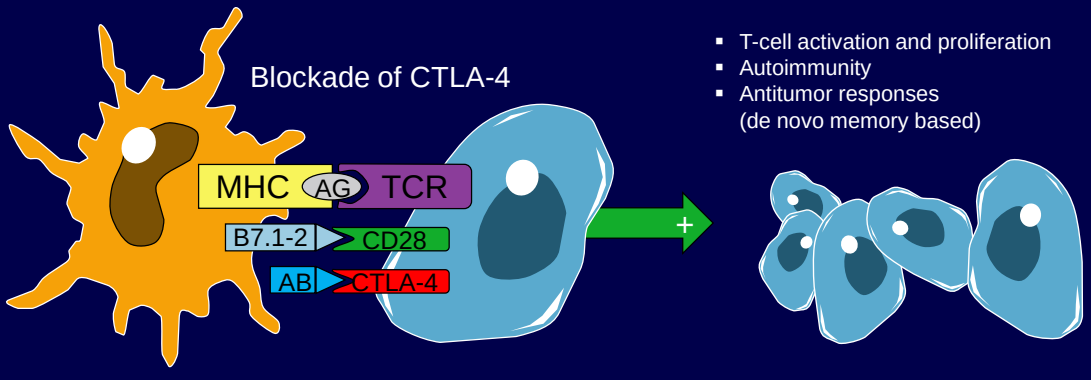
- Self-reactive T cells may proliferate when immune homeostasis or immune tolerance is disrupted
- Self-reactive T cells may react with normal tissue




Amos SM, et al. Blood. 2011;118:499-509.

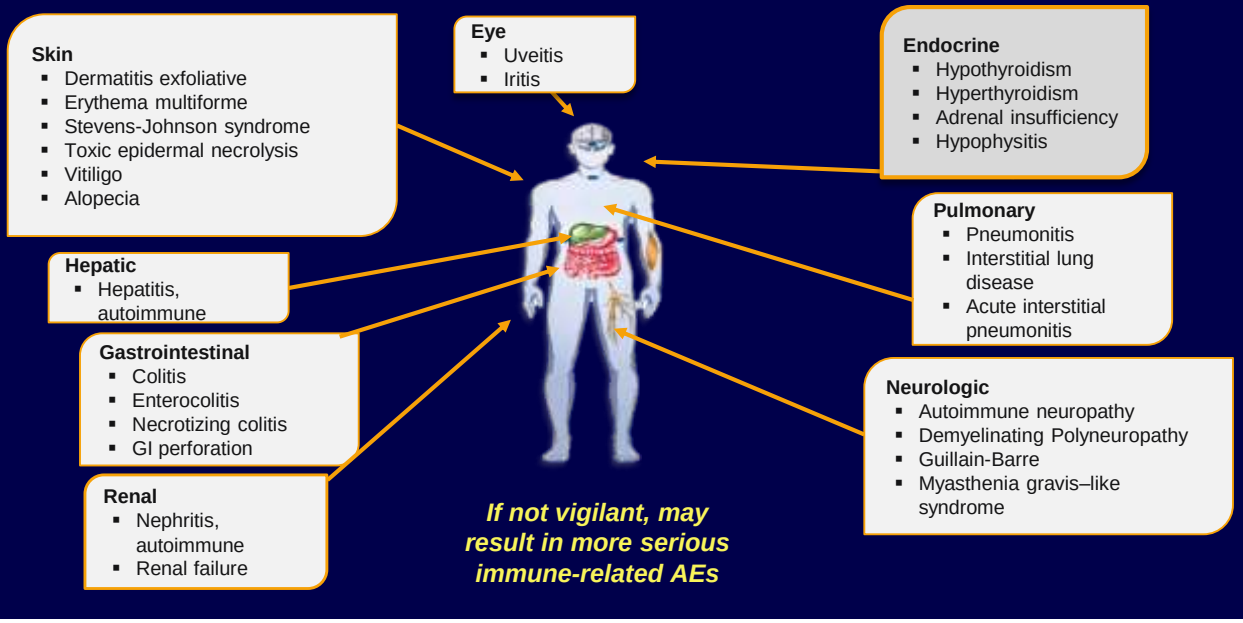
# irAEs: Mechanism of Action

- "Achilles heel" of checkpoint inhibitors: autoimmunity via irAEs
- Unique toxicities of immunomodulators caused by dysregulation of the host immune system, similar to autoimmune disease




Dillard T, et al. Pituitary. 2010;13:29-38.

# Immune-Related AEs With Immunotherapy

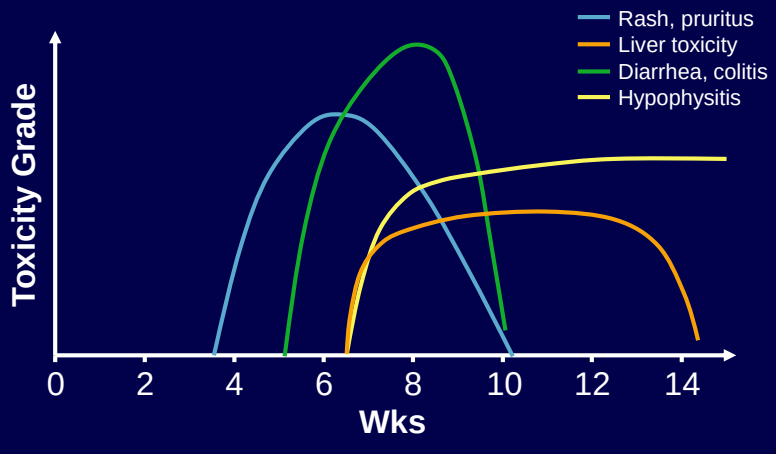


# irAEs: Considerations for Therapy

- Dose dependent
- Most irAEs develop during initial dosing period
  - Median time to onset: 5-9 wks
- Major categories of irAE associated with checkpoint inhibitors
  - Dermatologic
  - Gastrointestinal
  - Endocrine
  - Hepatic
- Graded by severity (CTCAE): 1 (mild) through 5 (death)
- Correlation between development of irAEs and treatment response
- Generally managed with use of corticosteroids or other immunosuppressive medications

Michot JM, et al. 2016 Eur J Cancer. 54:139-148.

# Kinetics of Appearance of irAEs With Ipilimumab




Combined analysis of 325 participants with 10 mg/kg IV q3w x 4

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.

# irAE Comparison: Ipilimumab and Nivolumab

- Difference in irAE incidence may be related to different sites of action

| irAE Category (All Grades), % | Ipilimumab[1] | Nivolumab[2] |
|---|---|---|
| Dermatologic | 43.5 | 37.4 |
| Gastrointestinal | 29 | 17 |
| Endocrine | 7.6 | 7.3 |
| Hepatic | 3.8 | 3.4 |
| Pulmonary | Not reported | 1.5 |

1. Hodi F, et al. N Engl J Med. 2010;363:711-723.
2. Robert C, et al. N Engl J Med. 2015;372:320-330.

# Combination Immunotherapy: irAEs

| Treatment-Related AEs, % | Ipilimumab + Nivolumab (n = 94) | | Ipilimumab + Placebo (n = 46) | |
|---|---|---|---|---|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Any tx-related AE | 91 | **54** | 93 | **24** |
| **Immune-related AEs** | | | | |
| ▪ Dermatologic | 71.3 | **9.6** | 58.7 | **0** |
| ▪ Gastrointestinal | 51.0 | **21.3** | 37 | **10.9** |
| ▪ Endocrine | 34.0 | **5.3** | 17.4 | **4.3** |
| ▪ Hepatic | 27.7 | **14.9** | 4.3 | **0** |
| ▪ Pulmonary | 11.7 | **2.1** | 4.3 | **2.2** |
| ▪ Renal | 3.2 | **1.1** | 2.2 | **0** |

Postow MA, et al. N Engl J Med. 2015;372:2006-2017.

# General Toxicity Management of Immune-Mediated Adverse Events

| Grade | Recommendation |
|---|---|
| 1 (mild) | Supportive care; may or may not withhold therapy |
| 2 (moderate) | Withhold therapy; may consider restarting therapy in future if resolves to grade ≤ 1<br>Low-dose corticosteroids (prednisone 0.5 mg/kg/day or equivalent) given if symptoms do not resolve in 1 wk |
| 3-4 (severe) | Discontinue therapy<br>Use high-dose corticosteroids (prednisone 1-2 mg/kg/day or equivalent) tapered **SLOWLY** over ≥ 1 mo once toxicity resolves to grade ≤ 1 |

# Will Steroids Make the Immunotherapy Stop Working Against Cancer?

- Studies suggest that immune suppression (eg, steroids) combats immune-mediated adverse reactions but does not reverse the antitumor effect of immune checkpoint agents

Troy ZH, et al. J Clin Oncol. 2015;33:3193-3198.

## Restarting Therapy After Treatment for Immune-Mediated Adverse Reaction

- Therapy can often be restarted after resolution of a grade 1-2 toxicity
- Permanent discontinuation of therapy often required in the case of a grade 3-4 toxicity
- The antitumor activity of immuno-oncology medications may persist long after drug discontinuation

## Key Takeaways for immune-mediated adverse reactions

- Autoimmunity has been associated with improved outcome in studies of some immune-based treatments
- Autoimmunity induced by current immune-based therapies is self-limited once the treatment has been discontinued
  - If toxicity not life-threatening, consideration may be given to reinstituting therapy once symptoms have resolved
- If the autoimmune toxicities are mild, symptoms can be managed medically while the patients remain on treatment
- Autoimmune adverse events may occur at anytime in the course of treatment

## Patient Question: What Can I Do to Mitigate the Risks of Side Effects?

- Cannot yet predict who will experience immune-mediated adverse reactions
- Reduce alcohol intake
- Avoid foods that are known to potentially cause stomach upset (eg, foods that are past expiration date, left out, too much fiber, too much grease)
- Report symptoms promptly!

## Patient Education on Novel Therapies

- Unique MOA and time to response
- Toxicity profiles differ from standard chemotherapy
  - Early recognition of irAEs essential
  - irAEs infrequent, treatable, and respond well to steroids
  - Whom and when to call for AEs
  - These new therapies are helping many people
- Reinforce teaching points at every point of contact
  - Notify healthcare team if the pt is admitted to another hospital

# Quizz Questions and Answers

1) Immunotherapy aims to boost immune activation against tumors by inhibition of anergic signals driven by CTLA-4 and PD-L1.

Answer: Yes

2) The expression of PD-L1 in immune cells is predictive of response to inhibitors of immune-checkpoints.

Answer: Yes

3) Adverse events to inhibitors of immune-checkpoints result from immune-mediated reactions and appear in the first two weeks of treatment.

Answer: No

# Take Home Messages

- Immune checkpoint inhibitors are a new standard of care for patients with cancer
- Assessing PD-L1 expression can provide information on potential efficacy for certain patient subsets
- The development of autoimmune phenomenon may be an expected toxicity associated with some immune-based therapies

# Thank You/Obrigado

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