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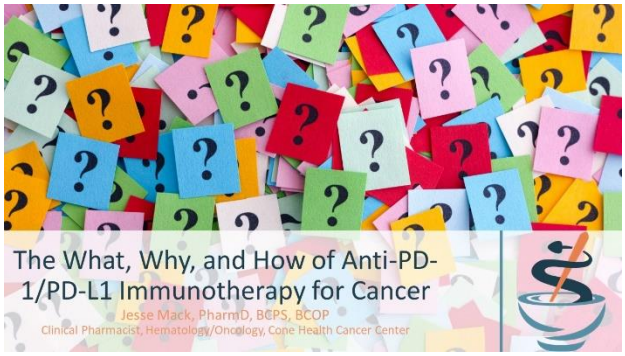
The What, Why, and How of Anti-PD-1/PD-L1 Immunotherapy for Cancer



Faculty
Jessica Mack, PharmD, BCPS, BCOP
Clinical Pharmacist, Hematology/Oncology,
Cone Health Cancer Center

The immune system is responsible for the recognition and clearance of malignant cells from the human body. This process involves a multitude of tightly controlled processes that allow actions to be taken on aberrant cells yet spares normal functioning of tissues. Immunotherapy refers to a class of medications and therapy modalities responsible for utilizing certain small molecules or receptors already involved in the immune system cascade or mimicking their actions. Once activated or reactivated, the immune system can target clinical cancerous lesions.
This program will highlight immunotherapy history and mechanisms employed in the aid of cancer eradication from the human body. FDA approved immunotherapy agents will be described including their mechanisms, indications for use, adverse event profile, and use in combination therapy. Future horizons of immunotherapeutic agents will be briefly reviewed.

Learning Objectives

Pharmacist

1. Recognize the role of the human immune system in the recognition and eradication of malignant cells from the body.
2. Distinguish between different mechanisms of action of immuno-oncology agents currently approved by the FDA for the treatment of malignancies.
3. List therapeutic indications of immunotherapy agents.
4. Identify adverse event profile of immunotherapy agents and treatment modalities employed for management of these toxicities.

Pharmacy Technician

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Nurse

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Target Audience

Pharmacists, Pharmacy Technicians, Nurses

Universal Activity Number

Pharmacist	Pharmacy Technician	Nurse
0798-0000-20-092-H01-P	0798-0000-20-092-H01-T	0798-0000-20-092-H01-N

Credit Hours

1.5 Hours

Activity Type

Knowledge-Based

CE Broker Tracking Number

20- 702555

Activity Release Date

June 9, 2020

Activity Offline Date

February 13, 2021

ACPE Expiration Date

June 2, 2023

Educational Support Provided By

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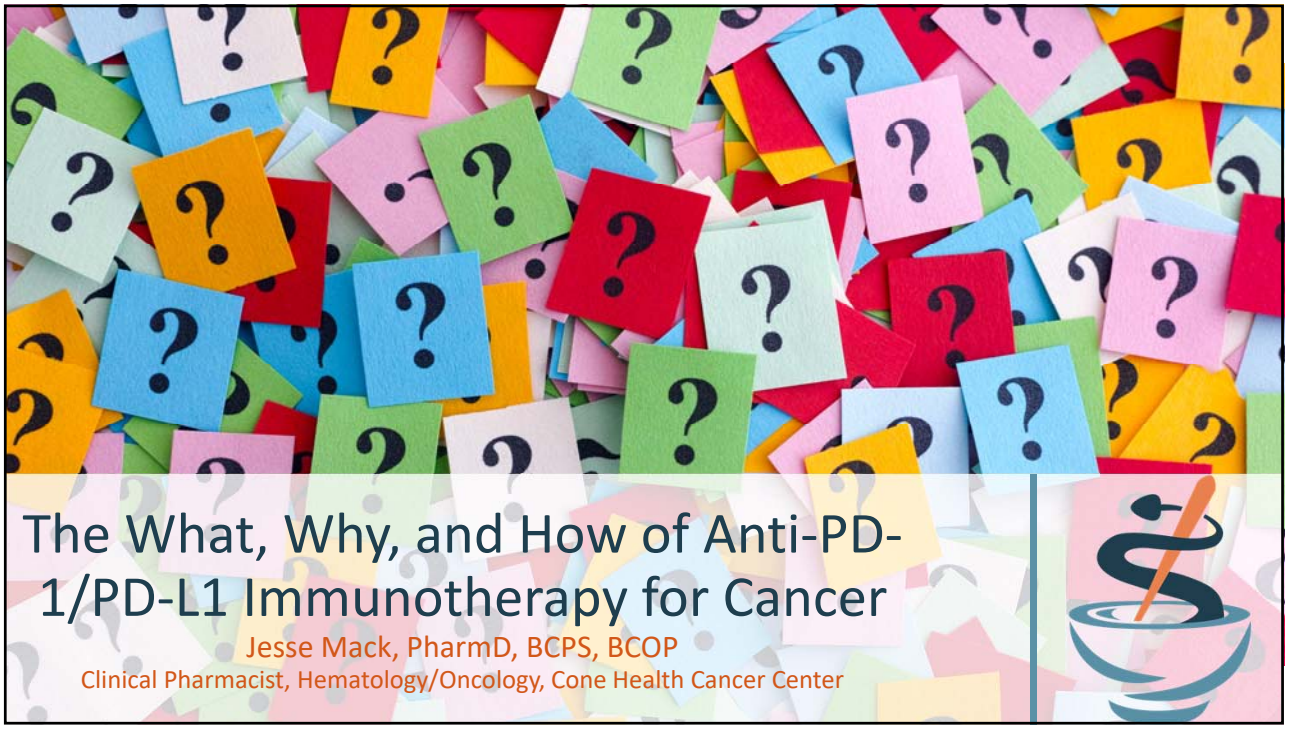

The What, Why, and How of Anti-PD-1/PD-L1 Immunotherapy for Cancer

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1

Faculty Disclosure

- [FACULTY] declares [no/a] existence of a financial interest in any amount related to the content of this activity.
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Learning Objectives

At the conclusion of this activity, participants should be better able to:

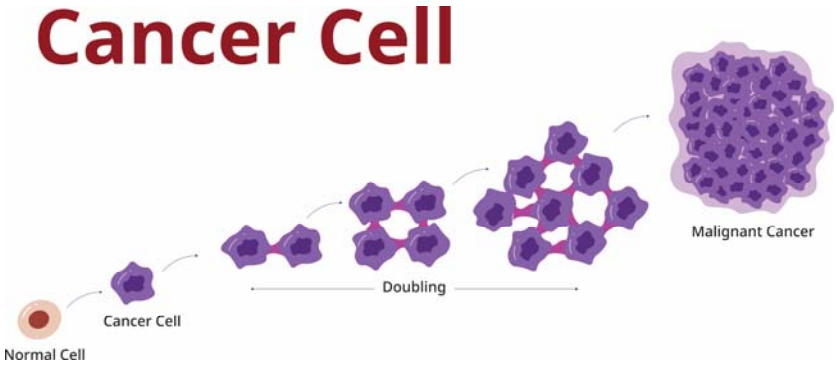
- Recognize the role of the human immune system in the recognition and eradication of malignant cells from the body.
- Distinguish between different mechanisms of action of immuno-oncology agents currently approved by the FDA for the treatment of malignancies.
- List therapeutic indications of immunotherapy agents.
- Identify the adverse event profile of immunotherapy agents and the treatment modalities employed for management of these toxicities.

3

What is Cancer?

4

Cancer Overview

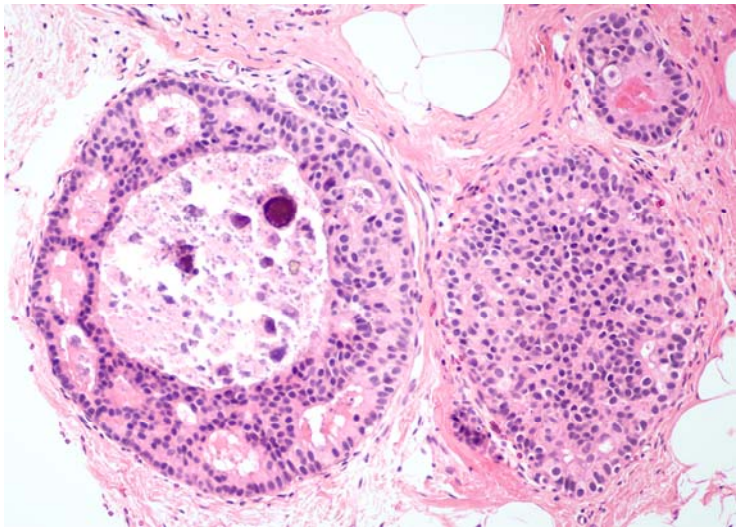


- Domenico Ribatti. The concept of immune surveillance against tumors: The first theories. *Oncotarget* 2017; 8(4): 7175-7180

5

Cancer Overview

- Breast Ductal Carcinoma
- Concentric shape of mammary ducts
- Increased population of cells compared to normal tissue



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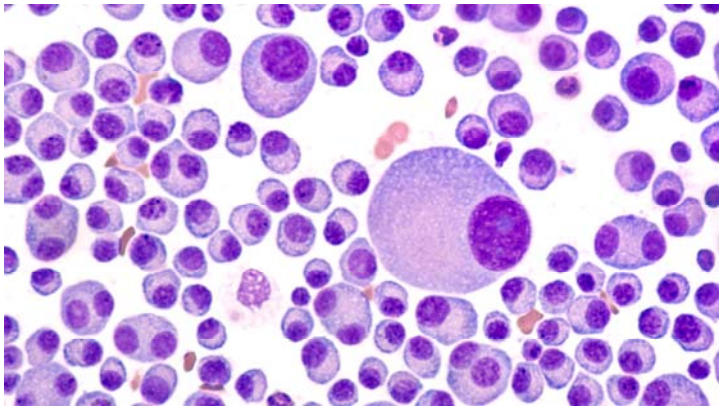
Cancer Overview

- Multiple Myeloma
- Malignancy of plasma B cells
- Large blood cells with defined nucleus and cytoplasm
- Undetectable nucleoli



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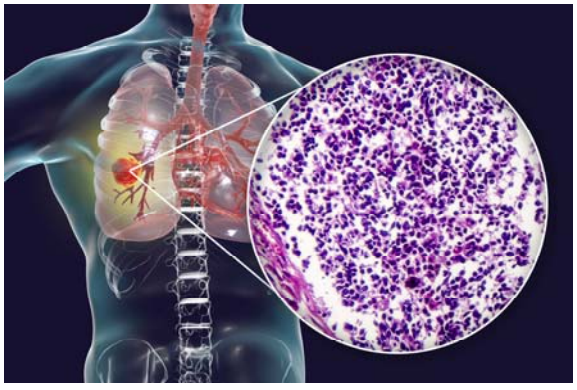
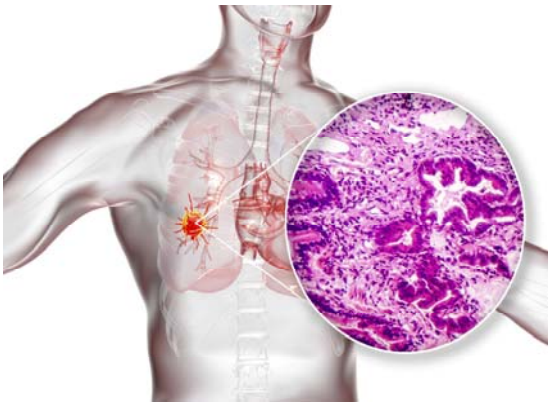
Cancer Overview



- Small Cell Lung Cancer
- Large population of abnormal cells
- Small cells, almost all nucleus
- Minimal cytoplasm seen

8

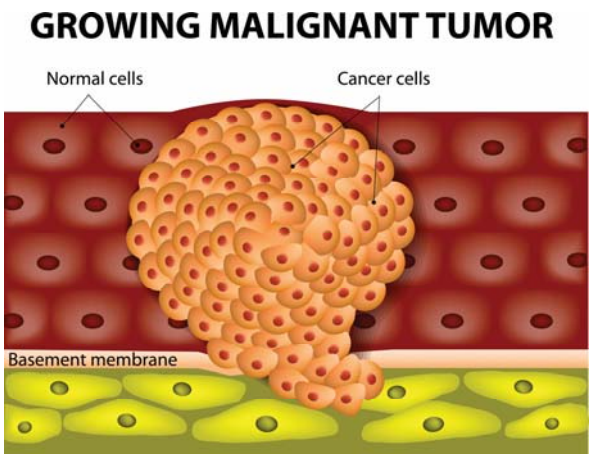
Cancer Overview



- Lung Adenocarcinoma
- Irregularly shaped gland-like structures

9

Cancer Overview



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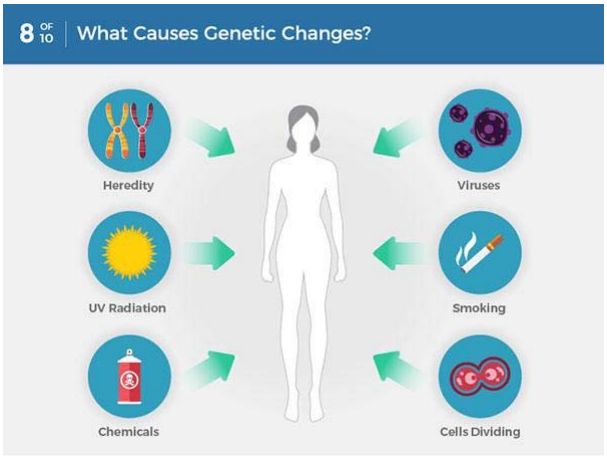
Cancer Development

- Genetic / Germline mutations
  - Inherited from parents' DNA
- Somatic mutations
  - Developed after birth due to DNA damage



- https://www.cancer.gov/about-cancer/understanding/what-is-cancer

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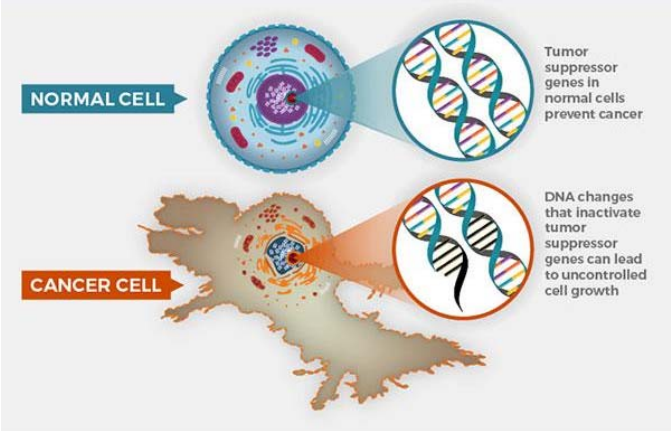
Suppressor Genes

- Tumor suppressor genes slow or stop cell growth
- DNA changes can lead to reduction in the transcription and activation of genes coding for tumor suppression and lead to uncontrolled cell growth



- https://www.cancer.gov/about-cancer/understanding/what-is-cancer

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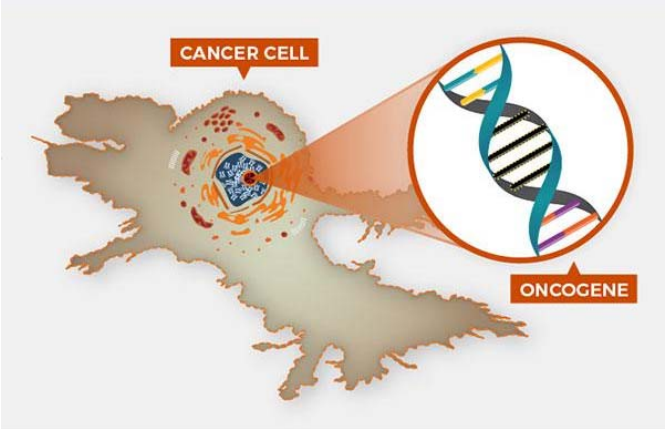
Oncogenes

- DNA changes can cause transcription and activation of oncogenes
- Oncogenes lead to uncontrolled cell growth, survival, and proliferation



- https://www.cancer.gov/about-cancer/understanding/what-is-cancer

13

Immunosurveillance

14

Immune System and Cancer

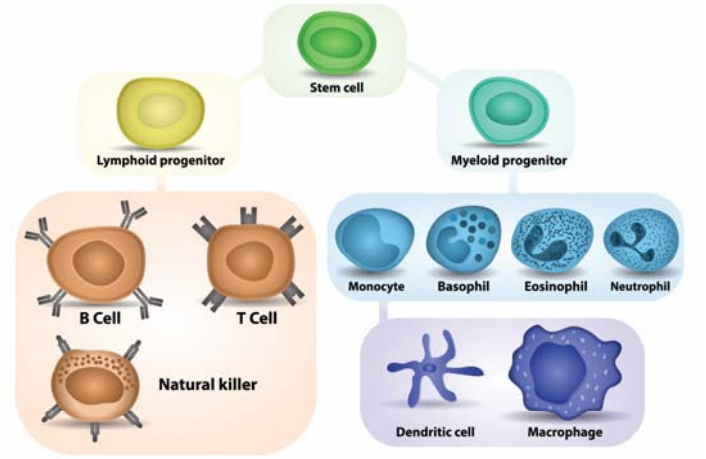
- Immunological Surveillance Mechanism
  - 1st documented in 1909
  - Scientifically proven in 1950's
- Immune system can recognize cancer as foreign and destroy cancer cells
- Led to hypothesis behind development of immunotherapy

- Burnet, M. Cancer-A Biological Approach. *Br Med J* 1957; 1(5023): 841-847
- Domenico Ribatti. The concept of immune surveillance against tumors: The first theories. *Oncotarget* 2017; 8(4): 7175-7180

15

Immune System Review

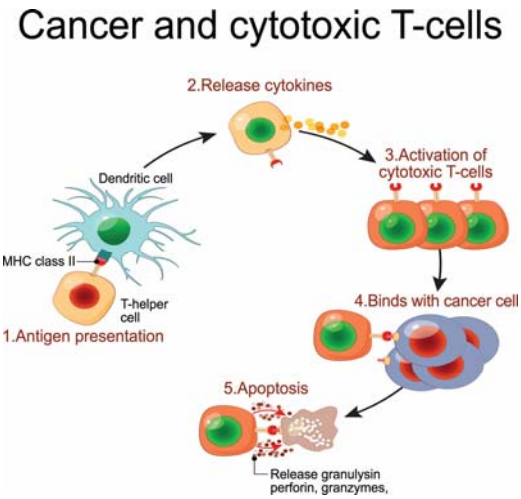
- Phagocytes
  - Monocytes
  - Neutrophils
  - Macrophages
- Dendritic cells
- Lymphocytes
  - B cells
  - T cells



- Chen, D. and Mellam, I. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* 2013; 39(1): 1-10

16

Immune System Review



- Chen, D. and Mellam, I. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* 2013; 39(1): 1-10

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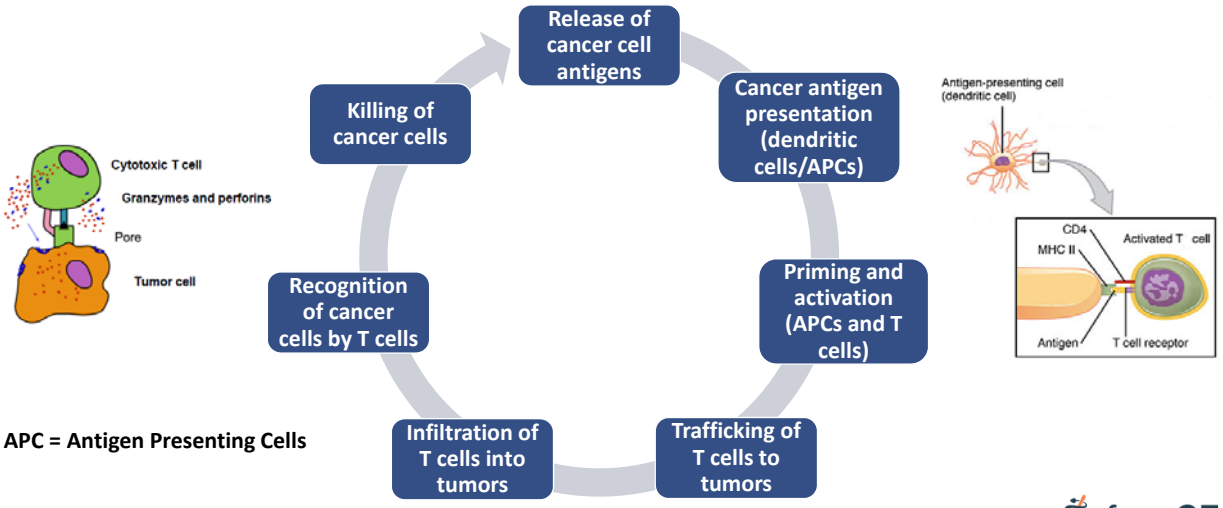
Cancer-Immunity Cycle



APC = Antigen Presenting Cells

- Adapted from Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013
- Adapted from https://commons.wikimedia.org/wiki/File:CD8%2B_T_cell_destruction_of_infected_cells.png
- Chen, D. and Mellam, I. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* 2013; 39(1): 1-10

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What is Immunotherapy?

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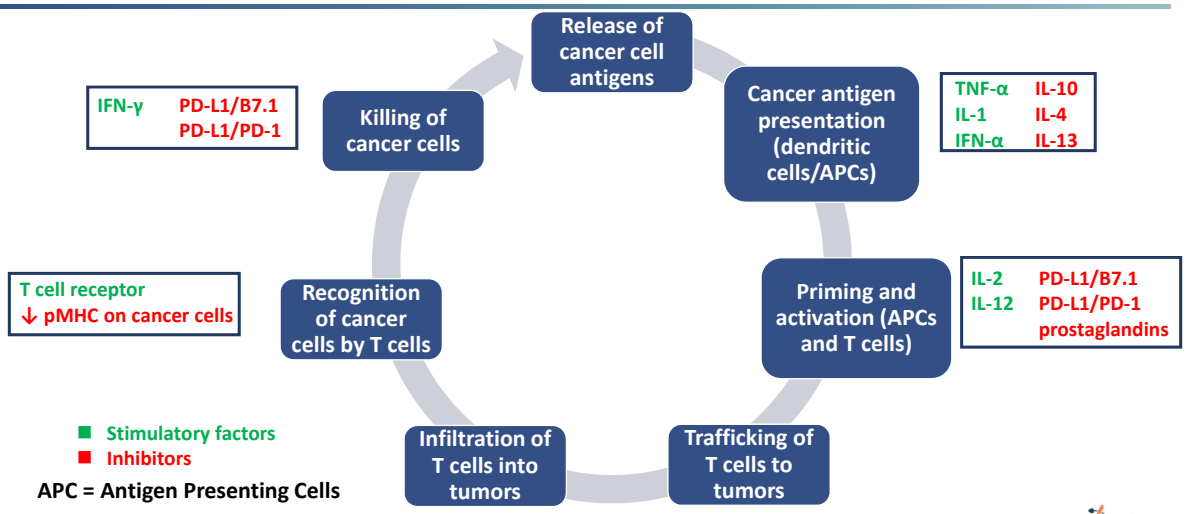
Immunotherapy

- Important advancement in cancer treatment
- Cancer is adaptable
  - Able to harbor new mutations leading to resistance of cancer treatments
- Immune system is adaptable
  - May be able to overcome resistance seen in fixed molecules

• Chen, D. and Mellam, I. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* 2013; 39(1): 1-10

20

Cancer-Immunity Cycle



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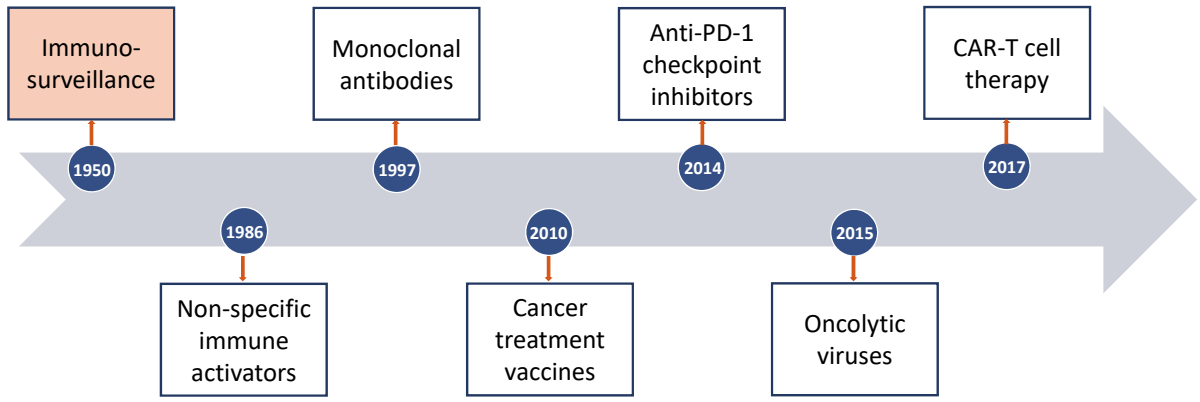
21

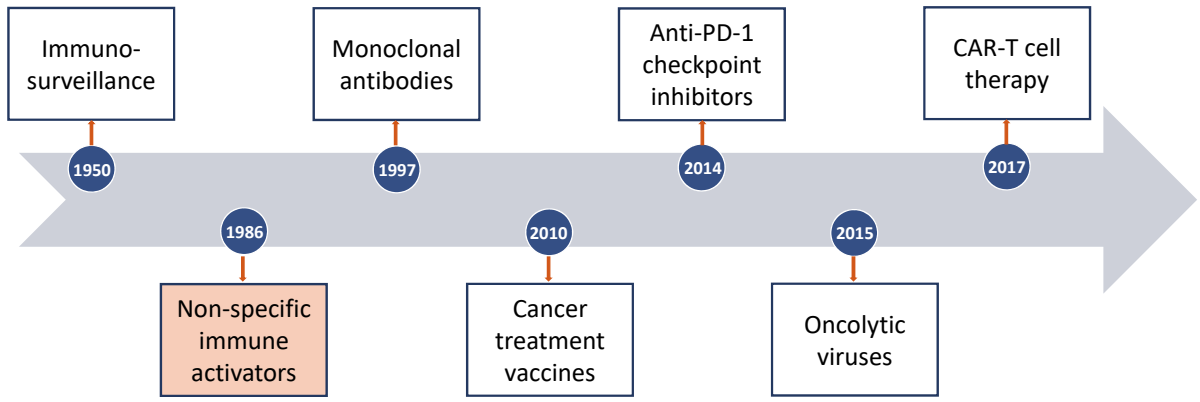
Immunotherapy Timeline



PD-1 = Programmed Death-1

22

Immunotherapy Timeline



PD-1 = Programmed Death-1

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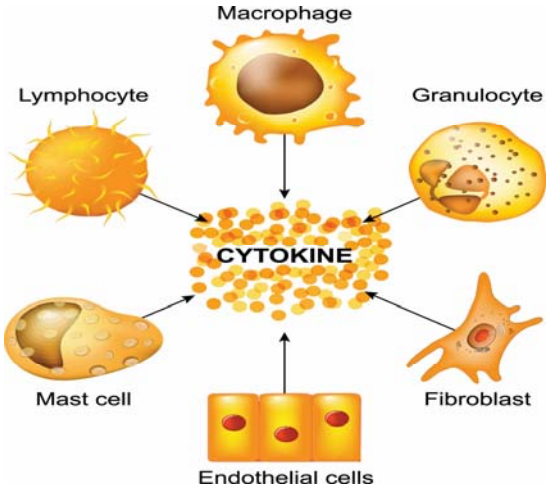
Non-Specific Immune Activation



- Cytokines produced by various cells
  - Interferon-alpha 2b
  - Aldesleukin (IL-2)
- Stimulate many points in immune system
- Activate T cells and B cells
- Increase vessel permeability
- Severe adverse effects

- Intron A [package insert]. Whitehouse Station, NJ: Merck & Co; 2018.
- Proleukin [package insert]. Emeryville, CA: Bayer HealthCare Pharmaceuticals; 2019.

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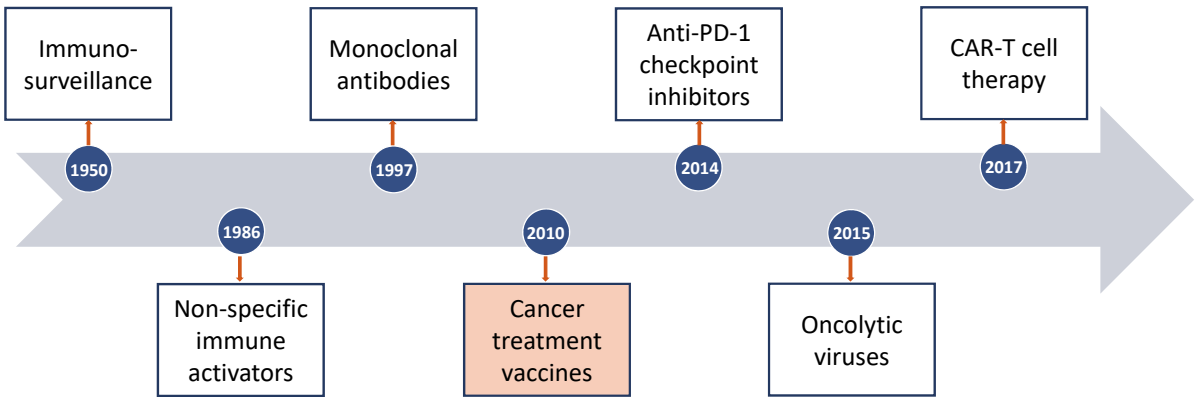
Immunotherapy Timeline



PD-1 = Programmed Death-1

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Cancer Treatment Vaccines

- Exposes immune system to cancer-specific antigen
- Tumor-specific immune response
- Spares normal tissue
- Difficult to predict extent of immune response
- Limited use currently
  - Sipuleucel-T (Provenge®) for prostate cancer, 2010

- Provenge [package insert]. Seal Beach, CA: Bayer Dendreon Pharmaceuticals LLC; 2014.

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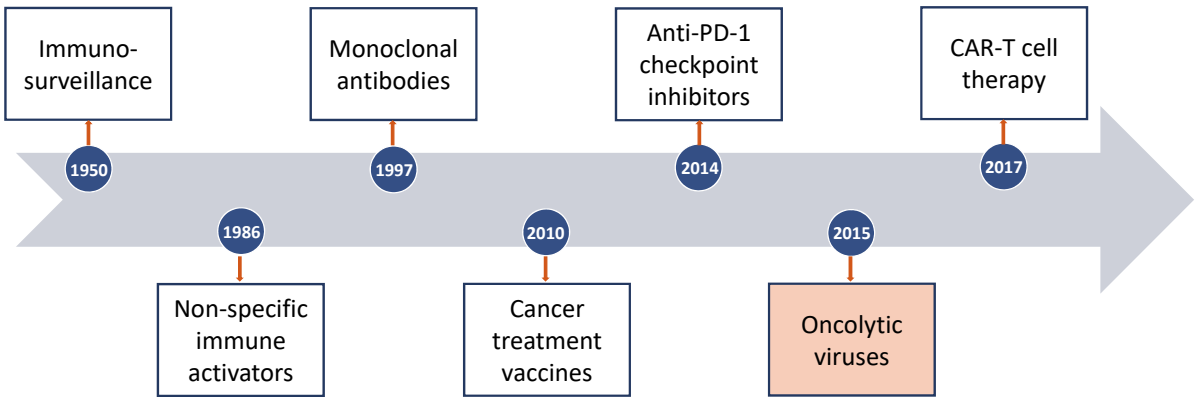
Immunotherapy Timeline



PD-1 = Programmed Death-1

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Oncolytic Viruses

- Engineered viruses that enter and replicate in cancer cells
- Spare normal tissue
- Lead to cancer cell lysing, spilling of tumor antigens into systemic circulation
- Limited use currently
  - Talimogene laherparepvec (Imlygic ®) for melanoma, 2015

- Imlygic [package insert]. Thousand Oaks, CA: Amgen, Inc; 2019.

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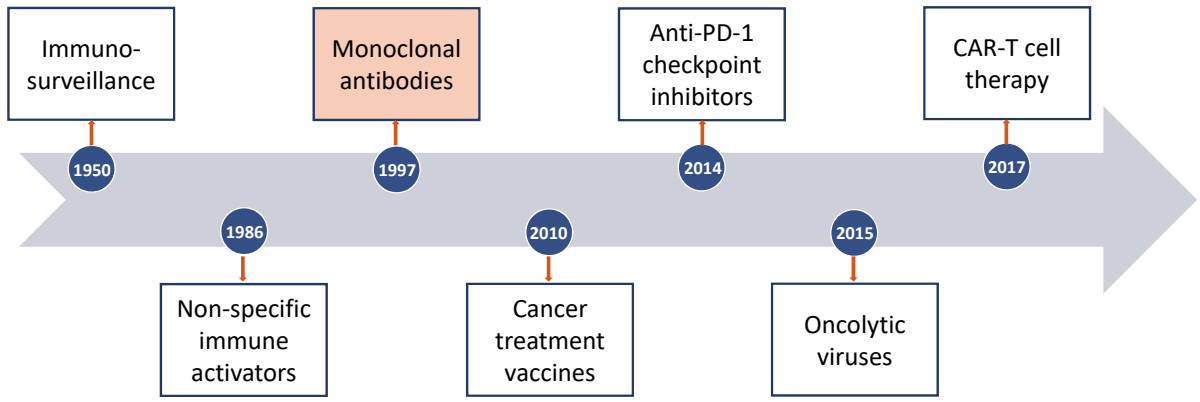
Immunotherapy Timeline



PD-1 = Programmed Death-1

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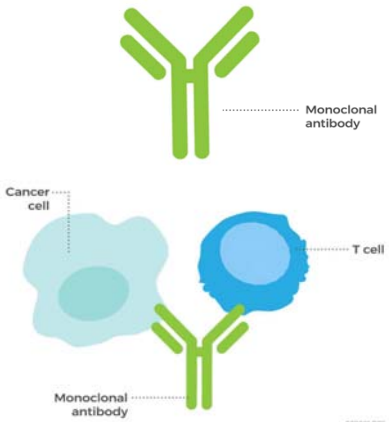
Monoclonal Antibodies

- Rituximab (Rituxan®)
  - Anti-CD20 antibody
  - Marks tumor cells for increased immune cell recognition
- Blinatumomab (Blincyto®)
  - Anti-CD19 and anti-CD3
  - Targets tumor cells and T cells
  - Direct placement of immune cell in contact with tumor cell

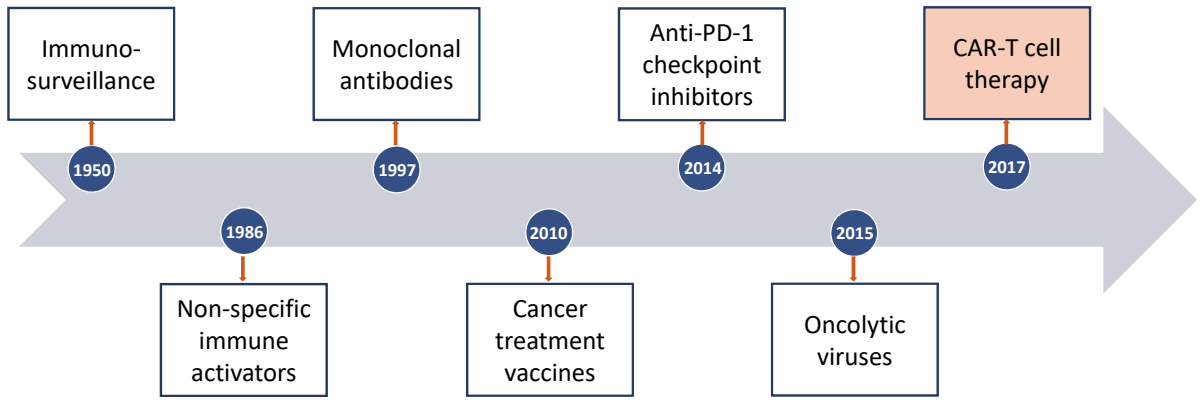


CD = Cluster of Differentiation

- https://www.cancer.gov/sites/g/files/xnrzdm211/files/styles/cgov_enlarged/public/cgov_image/media_image/2019-12/Monoclonal-antibodies-illustration.gif?itok=uHBwkVOH
- Blincyto [package insert]. Thousand Oaks, CA: Amgen, Inc; 2020.
- Rituxan [package insert]. South San Francisco, CA: Genentech, Inc; 2019.

30

Immunotherapy Timeline



PD-1 = Programmed Death-1

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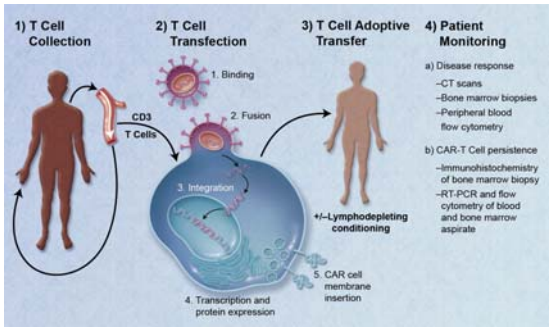
T-Cell Transfer Therapies

- Chimeric antigen receptor T cells
- CAR-T cells
  - Harvest patient T cells
  - Insert tumor specific receptor into T cell outer membrane
  - T cell expansion
  - Engineered T cell infusion
  - Serious adverse event profile
    - Cytokine storm
    - CNS toxicity



- Caron A. Jacobson and Jerome Ritz - http://bloodjournal.hematologylibrary.org/content/118/18/4761.full

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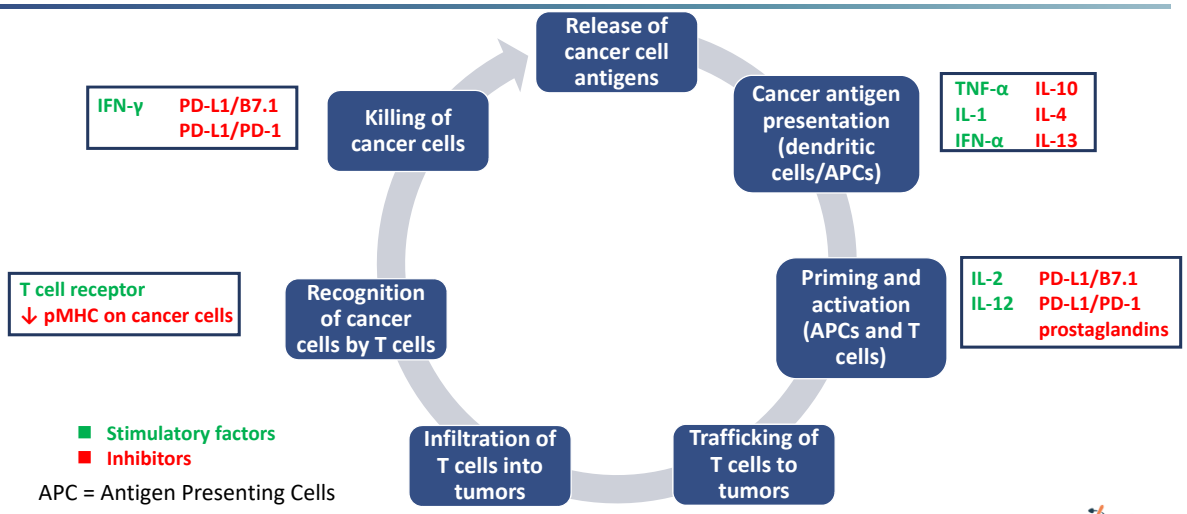
Cancer-Immunity Cycle



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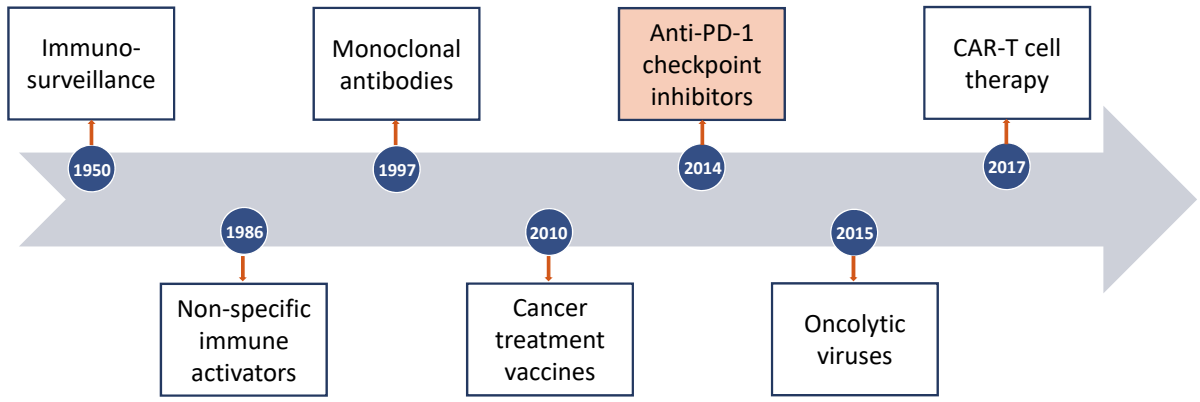
Immunotherapy Timeline



PD-1 = Programmed Death-1

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Immune Checkpoints

- Immune system can recognize and eradicate cancer
- Immune system must maintain balance between foreign destruction and auto-immune destruction
- Immune checkpoints can halt immune responses
- Tumors can exploit these checkpoints to evade immune response
- Programmed Cell Death-1 Pathway

- Chen, D., et al. Molecular Pathways: Next-Generation Immunotherapy - Inhibiting Programmed Death-Ligand 1 and Programmed Death-1. *Cancer Res* 2012; 18(24): 6580-6587
- Chen, D. and Mellam, I. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* 2013; 39(1): 1-10

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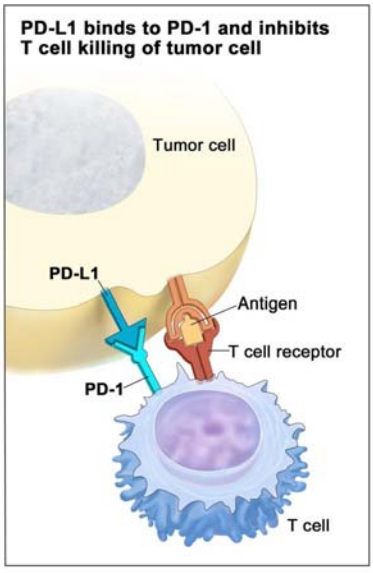
Programmed Cell Death-1

- Membrane bound T cell checkpoint receptor, PD-1
- 2 ligands
  - Programmed Death Ligand 1, PD-L1
    - Produced by a variety of cells
    - Over expressed in 20-50% of human cancers
  - Programmed Death Ligand 2, PD-L2
    - Produced by limited cells
- Receptor-ligand interaction dampens T cell response
  - ↓ cytokine production, ↓ T cell proliferation



- Chen, D., et al. Molecular Pathways: Next-Generation Immunotherapy - Inhibiting Programmed Death-Ligand 1 and Programmed Death-1. *Cancer Res* 2012; 18(24): 6580-6587

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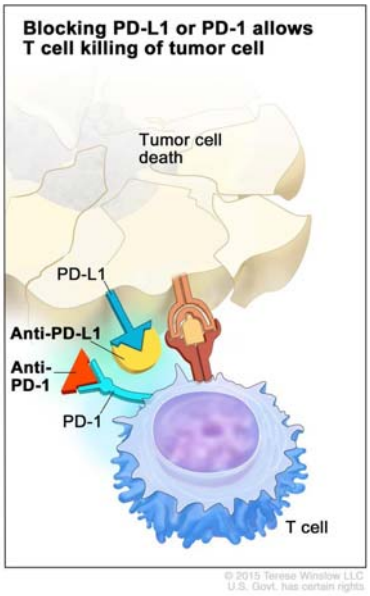
Anti-PD-1 Therapy

- Block interaction of receptor and ligand
- Restore normal T cell functioning
- Remove immune breaks and activity is quickly restored
- Durable responses
- Increased tolerability when compared to cytotoxic chemotherapy



- Chen, D., et al. Molecular Pathways: Next-Generation Immunotherapy - Inhibiting Programmed Death-Ligand 1 and Programmed Death-1. *Cancer Res* 2012; 18(24): 6580-6587

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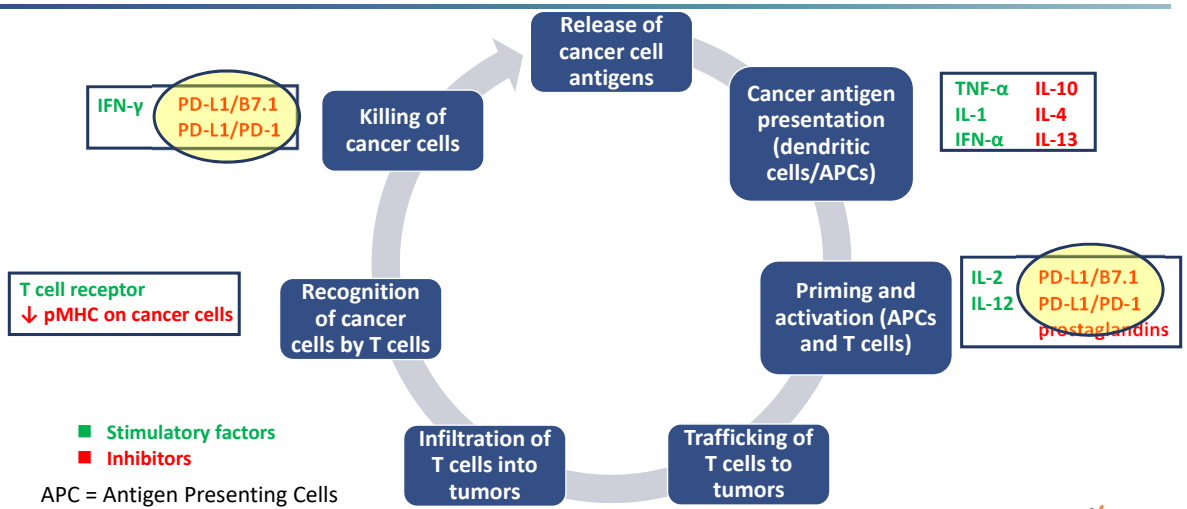
Cancer-Immunity Cycle



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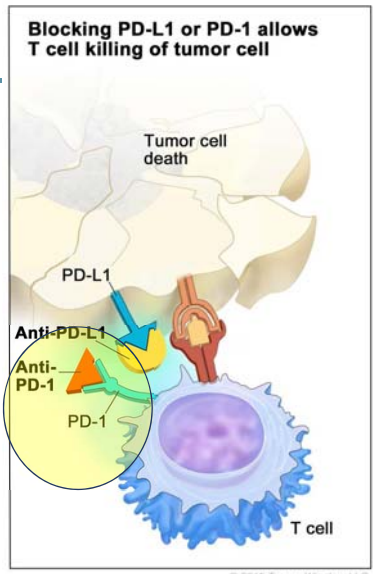
Anti-PD-1

- Target PD-1 receptor on T cells
- Block binding of PD-L1 and PD-L2
- Can saturate T cells
- Increased potential of auto-immune toxicity
  - Increased rate of pneumonitis



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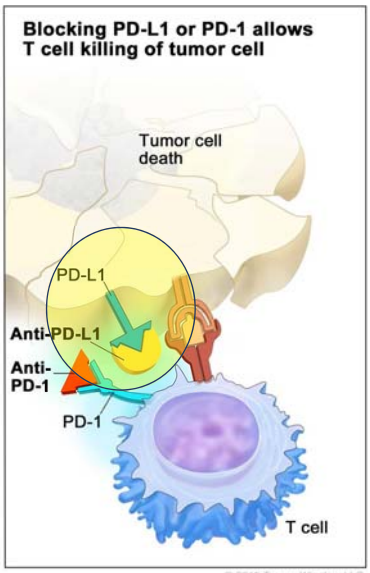
Anti-PD-L1

- Target only PD-L1 binding to receptors
- Removes inhibitory actions from PD-L1 binding at other receptors
- Decreases lung related toxicity compared to full PD-1 blockade
- High concentrations needed for clinical benefit
  - Unable to concentrate in CNS



PD-L1 = Programmed Death Ligand-1

- Chen, D., et al. Molecular Pathways: Next-Generation Immunotherapy - Inhibiting Programmed Death-Ligand 1 and Programmed Death-1. *Cancer Res* 2012; 18(24): 6580-6587

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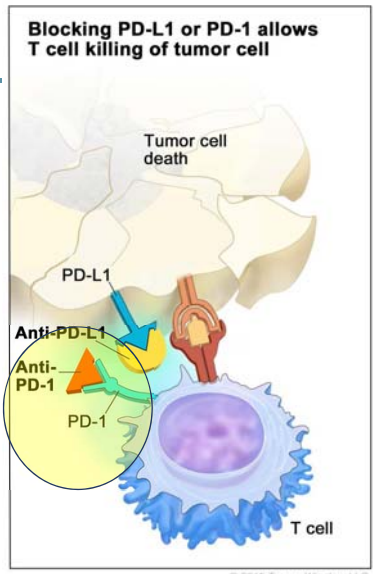
Anti-PD-1 Agents

- Nivolumab (Opdivo®)
- Pembrolizumab (Keytruda®)
- Cemiplimab (Libtayo ®)



PD-1 = Programmed Death-1

- Fessas, P., et al. A Molecular and Preclinical Comparison of the PD-1-Targeted T-cell Checkpoint Inhibitors Nivolumab and Pembrolizumab. *Semin Oncol* 2017; 44(2): 136-140

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Nivolumab (Opdivo®)

- Human IgG4 monoclonal antibody that binds PD-1 receptor
- December 22, 2014: Original accelerated approval
  - 2nd line metastatic melanoma, ORR 37.1%
  - 3 mg/kg IV every 2 weeks over 60 minutes
- September 2016: 240 mg every 2 weeks flat dosing
- January 2018: 30-minute infusion
- March 2018: 480 mg every 4 weeks flat dosing (AWP $15,792)

PD-1 = Programmed Death-1
ORR = Overall Response Rate

- Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

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Nivolumab (Opdivo®)

Front-Line Use	2nd Line Use	Other Uses
• Unresectable / Metastatic Melanoma • Adjuvant Melanoma • Advanced Renal Cell Carcinoma + ipilimumab	• Metastatic Non-Small Cell Lung Cancer (NSCLC) • Metastatic Renal Cell Carcinoma • Recurrent / Metastatic Head & Neck Cancer • Advanced / Metastatic Urothelial Carcinoma • Hepatocellular Carcinoma • Some Metastatic Colorectal Cancers (MSI-H)	• Relapsed / Refractory Classical Hodgkin Lymphoma • Metastatic Small Cell Lung Cancer (SCLC)

• Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

43

Pembrolizumab (Keytruda®)

- Human IgG4 monoclonal antibody that binds PD-1 receptor
- September 4, 2014: Original accelerated approval
  - 2nd line metastatic melanoma, ORR 23.6%
  - 2 mg/kg IV every 3 weeks over 30 minutes
- August 2016: 200 mg every 3 weeks flat dosing
- April 2020: 400 mg every 6 weeks flat dosing (AWP $23,337)

PD-1 = Programmed Death-1
ORR = Overall Response Rate

• Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co; 2020.

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Pembrolizumab (Keytruda®)

Front-Line Use

- Unresectable / Metastatic Melanoma
- Adjuvant Melanoma
- Metastatic NSCLC + chemotherapy
- Unresectable / Metastatic NSCLC (≥1% PD-L1 expression)
- Metastatic Head & Neck Cancer + chemotherapy
- Metastatic Head & Neck Cancer (≥1% PD-L1 expression)
- Advanced / Metastatic Urothelial Carcinoma (≥10% PD-L1 expression)
- Advanced / Metastatic Merkel Cell Carcinoma
- Advanced Renal Cell Carcinoma + axitinib

• Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co; 2020.

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Pembrolizumab (Keytruda®)

2nd Line Use

- Metastatic NSCLC (≥1% PD-L1 expression)
- Recurrent / Metastatic Head & Neck Cancer
- Advanced / Metastatic Urothelial Carcinoma
- Some MSI-H / dMMR Metastatic Cancers
- Advanced / Metastatic Esophageal Squamous Cell Carcinoma (≥10% PD-L1 expression)
- Recurrent / Metastatic Cervical Cancer (≥1% PD-L1 expression)
- Hepatocellular Carcinoma
- Advanced Endometrial Carcinoma + lenvantinib

• Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co; 2020.

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Pembrolizumab (Keytruda®)

Other Uses

- Relapsed / Refractory Classical Hodgkin Lymphoma
- Relapsed / Refractory Primary Mediastinal Large B-Cell Lymphoma
- Metastatic SCLC
- Advanced / Metastatic Gastric Cancer (≥1% PD-L1 expression)

- Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co; 2020.

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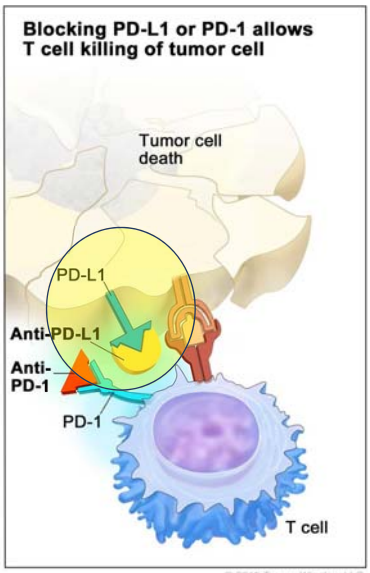
Anti-PD-L1 Agents

- Atezolizumab (Tecentriq®)
- Avelumab (Bavencio®)
- Durvalumab (Imfinzi®)



PD-L1 = Programmed Death Ligand-1

- Chen, D., et al. Molecular Pathways: Next-Generation Immunotherapy - Inhibiting Programmed Death-Ligand 1 and Programmed Death-1. *Cancer Res* 2012; 18(24): 6580-6587

48

Atezolizumab (Tecentriq®)

- Humanized IgG1 mAb that binds PD-L1
  - Prevents ligand interaction with PD-1 and B7.1
- May 18, 2016: Original accelerated approval
  - 2nd line metastatic urothelial carcinoma
    - ORR 26.0% with PD-L1 expression in > 5% tumor infiltrating immune cells
  - 1200 mg IV every 3 weeks over 60 minutes (AWP $11,032)
  - 840 mg IV every 2 weeks over 60 minutes

PD-L1 = Programmed Death Ligand-1
ORR = Overall Response Rate

- Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc; 2019.

49

Atezolizumab (Tecentriq®)

Front-Line Use	2nd-Line Use
• Advanced / Metastatic Urothelial Carcinoma • Metastatic Nonsquamous NSCLC + chemotherapy +/- bevacizumab • Metastatic Triple Negative Breast Cancer + chemotherapy (≥1% PD-L1 expression) • Extensive Stage SCLC + chemotherapy	• Advanced / Metastatic Urothelial Carcinoma • Metastatic NSCLC

- Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc; 2019.

50

Avelumab (Bavencio®)

- Human IgG1 mAb that binds PD-L1
  - Prevents ligand interaction with PD-1 and B7.1
- March 23, 2017: Original accelerated approval
  - Front line metastatic Merkel Cell Carcinoma
- 800 mg IV every 2 weeks over 60 minutes (AWP $7,777)
- Premedication for at least 1st 4 doses
  - Antihistamine and acetaminophen

PD-L1 = Programmed Death Ligand-1

- Bavencio [package insert]. Rockland, MA: EMD Serono; 2019.

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Avelumab (Bavencio®)

Front-Line Use	2nd-Line Use
• Metastatic Merkel Cell Carcinoma • Advanced Renal Cell Carcinoma + axitinib	• Advanced / Metastatic Urothelial Carcinoma

- Bavencio [package insert]. Rockland, MA: EMD Serono; 2019.

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Durvalumab (Imfinzi®)

- Human, engineered IgG1 mAb that binds PD-L1
  - Prevents ligand interaction with PD-1 and B7.1
- May 1, 2017: Original accelerated approval
  - 2nd line metastatic urothelial carcinoma
- 10 mg/kg IV every 2 weeks over 60 minutes
- 1500 mg IV every 3 weeks over 60 minutes (AWP $8,796)

PD-L1 = Programmed Death Ligand-1

- Imfinzi [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2020.

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Durvalumab (Imfinzi®)

Front-Line Use	2nd-Line Use
• Consolidation Treatment of Unresectable Stage III NSCLC Without Progression after Concurrent Chemoradiation • Extensive Stage SCLC + chemotherapy	• Advanced / Metastatic Urothelial Carcinoma

- Imfinzi [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2020.

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Immune Checkpoint Inhibition Response Rates

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PD-1 Agent Response Rates

- All-comers 13-38%
- Increased in tumors that rely on ↑ PD-L1 expression to evade immune response
- Increased in tumors with ↑ immunogenicity, tumor mutational burden
  - Microsatellite instability – high
  - Deficient in mismatch repair enzymes
- Combining immune checkpoint inhibitors (ICPi) with other treatment modalities may increase response rates

PD-L1 = Programmed Death Ligand-1

- Chen, D., et al. Molecular Pathways: Next-Generation Immunotherapy - Inhibiting Programmed Death-Ligand 1 and Programmed Death-1. *Cancer Res* 2012; 18(24): 6580-6587

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Checkpoint Inhibitors + Chemotherapy or Radiation

ORR = Overall Response Rate
PFS = Progression Free Survival

Cytotoxic chemotherapy destroys tumor cells

- Increased release of tumor antigens
- Increased tumor specific immune response

Pembrolizumab + carboplatin & paclitaxel

- Front-line treatment of metastatic non small cell lung cancer, ORR 58%

Atezolizumab + protein-bound paclitaxel

- Front line treatment of locally advanced or metastatic TNBC, PD-L1 +, ORR 53%

Abscopal effect with radiation

- Durvalumab consolidation therapy in unresectable stage III NSCLC following definitive concurrent chemoradiation, PFS 16.8 mo vs 5.6 mo

- Cushman T., et al. Combining Radiation Plus Immunotherapy to Improve Systemic Immune Response. *J Thorac Dis* 2018; Suppl 3: S468-S479
- Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co; 2020.
- Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc; 2019.

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Checkpoint Inhibitors + Small Molecule Inhibitors

Some tyrosine kinase inhibitors modulate immune responses

Can be used in combination with ICPi to increase tumor-specific immune responses

Vascular Endothelial Growth Factor therapy (VEGF)

- VEGF can ↑ PD-L1 production and PD-1 expression, ↓ differentiation to T cells
- Blocking VEGF receptor or ligands can reverse these actions

Pembrolizumab + lenvantinib for endometrial cancer, ORR 38.3%

Axitinib + pembrolizumab (ORR 59%) or avelumab (ORR 51.7%) for RCC

ORR = Overall Response Rate

- Bavencio [package insert]. Rockland, MA: EMD Serono; 2019.
- Inlyta [package insert]. NY, NY: Pfizer Inc; 2020.
- Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co; 2020.
- Lenvima [package insert]. Woodcliff Lake, NJ: Eisai, Inc; 2020.

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Combination Dual Checkpoint Inhibitors

PD-1 = Programmed Death-1
ORR = Overall Response Rate

- Anti-PD-1 + anti-cytotoxic T lymphocyte antigen-4 (CTLA-4)
- CTLA4 is a major negative regulator of T cells
  - Blocking CTLA-4 promotes T cell activation, non-specific T cell expansion
- Ipilimumab (Yervoy®) only FDA approved anti-CTLA-4 agent
- Increased response rates over nivolumab monotherapy
  - Some colorectal cancers, ORR 49%
  - Hepatocellular carcinoma, ORR 33%
  - Renal cell carcinoma, ORR 41.6%
- Non-specific immune activation increases severe ADEs

- Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.
- Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

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Immune Checkpoint Inhibitors: Adverse Effects

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Immune-Mediated ADEs

- Differs from side effect profile of cytotoxic chemotherapy
  - Examples: vomiting, alopecia, mucositis, febrile neutropenia
- Result of auto-immune destruction of tissues
- On-target effects, due to primary mechanism
- Class effect, consistent treatment recommendations regardless of offending agent
- Most common: skin reaction, GI toxicity
- Others: lung inflammation, hypo- or hyper-thyroid
- Rapid intervention and management prevents serious damage

- Brahmer, J., et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2018; 36(17): 1714-1768

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Immune-Mediated ADEs

- Serious ADEs
  - Clinically significant endocrinopathies, 10%
    - Hypophysitis
    - Diabetes
    - Primary adrenal insufficiency
  - Nephritis
  - Hepatitis
  - Auto-immune hemolytic anemia or thrombocytopenia
  - Pure red cell aplasia

- Brahmer, J., et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2018; 36(17): 1714-1768

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Treatment of Immune-Mediated ADEs

Checkpoint inhibitor dose reduction strategies are not used

Agents to dampen immune response

- Non-specific immunosuppressants (steroids)
- Specific immunosuppressants (infliximab)

Decrease in immune response rapid following treatment administration

- Brahmer, J., et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2018; 36(17): 1714-1768

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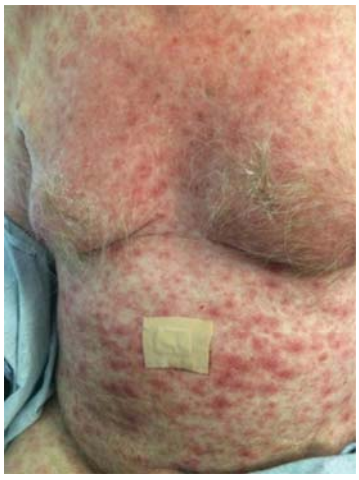
Dermatitis – Case Example

- JB is a 74yo male with metastatic urothelial carcinoma, previous cisplatin
- Pembrolizumab (Keytruda®) 200 mg every 3 weeks x 4 doses
- Pembrolizumab (Keytruda®) 400 mg every 6 weeks x 2 doses
- Progressive rash on trunk, spreading to extremities



- https://www.cancer.gov_contextual_image/100/200/2/files/man-with-severe-rash-across-chest-and-stomach-article.jpg?h=8dbdf7bd&itok=MvtFoEJb

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Dermatitis

Grading	Management
Grade 1 Symptoms do not affect QoL	•Continue ICPi •Low dose topical corticosteroids
Grade 2 Affects QoL, Requires intervention	•Consider holding ICPi until Grade 1 •Consider 1-2 mg/kg prednisone taper
Grade 3 Affects quality of life Refractory to interventions	•Hold ICPi •Consider dermatology consult •Initiate 1-2 mg/kg prednisone taper
Grade 4 Severe rash, intolerable Unmanageable with prior interventions	•Hold /discontinue ICPi •Urgent dermatology consult •Initiate 1-2 mg/kg prednisone taper

QoL = Quality of Life
ICPi = Immune Checkpoint inhibitor

- Brahmer, J., et al. Managemen/sites/g/files/xnrzdm211/files/styles/cgov_article/public/cgovt of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2018; 36(17): 1714-1768

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Colitis

ICPi = Immune Checkpoint inhibitor

Grading	Management
Grade 1 < 4 stools/day above baseline	•Continue ICPi •Symptom management, fluid/electrolyte replacement •Consider GI consult for prolonged cases
Grade 2 4-6 stools/day above baseline	•Hold ICPi until Grade 1 •GI consult •Consider 1-2 mg/kg prednisone taper
Grade 3 ≥ 7 stools/day above baseline, incontinence Hospitalization indicated	•Hold ICPi and consult GI •Initiate 1-2 mg/kg prednisone taper •No improvement in 3-5 days, initiate IV corticosteroids or non-steroid agent (infliximab)
Grade 4 Life-threatening consequences Urgent intervention indicated	•Permanently discontinue ICPi, urgent GI consult •Initiate 1-2 mg/kg prednisone, start taper after 4-6 weeks of steroid treatment, initiate alternate agents as indicated

- Brahmer, J., et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2018; 36(17): 1714-1768

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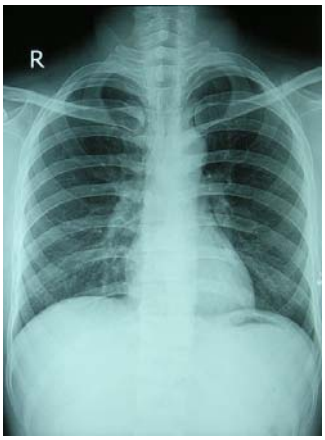
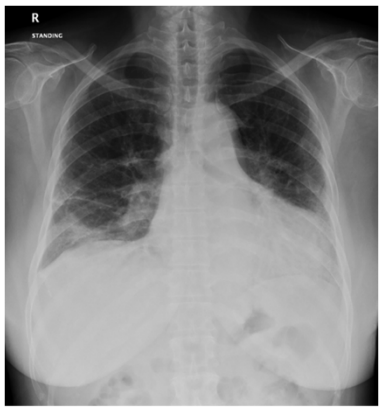
Pneumonitis





- https://commons.wikimedia.org/wiki/File:Chest_X-ray_2346.jpg
- https://commons.wikimedia.org/wiki/File:Acute_interstitial_pneumonitis_3.png

67

Pneumonitis

ICPi = Immune Checkpoint inhibitor
ADL = Activities of Daily Living

Grading	Management
Grade 1 Asymptomatic, confined to one lobe or <25% total lung parenchyma	•Hold ICPi •Repeat imaging in 3-4 weeks, can restart ICPi if noted improvement
Grade 2 Symptomatic, limiting ADLs, involves >1 lobe or 25-50% total lung parenchyma	•Hold ICPi until Grade 1 •Initiate 1-2 mg/kg prednisone, taper by 5-10 mg/week over 4-6 weeks •Monitor every 3 days
Grade 3 Severe symptoms, hospitalization required, involves all lobes or > 50% total lung parenchyma	•Permanently discontinue ICPi •Empiric antibiotics, initiate 1-2 mg/kg methylprednisolone •No improvement in 48 hr, initiate infliximab or mycophenolate, or IVIG, or cyclophosphamide. 4-6 week steroid taper
Grade 4 Life-threatening respiratory compromise, urgent intervention indicated (intubation)	•Management per Grade 3 recommendations

- Brahmer, J., et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2018; 36(17): 1714-1768

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Thyroiditis

ICPi = Immune Checkpoint inhibitor

Primary Hypothyroidism	
TSH < 10 mU/L & asymptomatic	•Continue ICPi •Monitor TSH every 4-6 weeks
TSH > 10 mU/L & moderate symptoms	•Consider holding ICPi •Initiate thyroid replacement •Long-term replacement expected •Goal TSH < 10 mU/L
Hold or continue ICPi therapy?	Based on symptom severity
Primary Hyperthyroidism	•Short-lived •Manage symptoms (beta-blockers, hydration)

- Brahmer, J., et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2018; 36(17): 1714-1768

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Steroid Immunosuppression

- Rapid response to treatment
- Inhibits vasodilation, decreases permeability of blood vessels
- Decreases cellular differentiation
- Decreases cytokine production
- Increases T cell apoptosis
- Steroid treatment course based on severity of symptoms, risk/benefit of prolonged use

- Coutinho, A. and Chapman, K. The Anti-Inflammatory and Immunosuppressive Effects of Glucocorticoids, Recent Developments and Mechanistic insights. *Mol Cell Endocrinol* 2011; 335(1): 2-13

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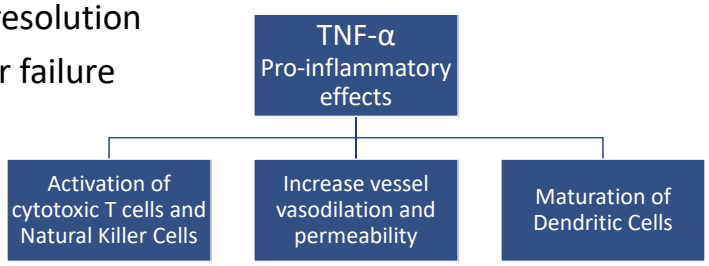
Infliximab Immunosuppression

- Infliximab (Remicade®)
- Human-murine chimeric IgG1 monoclonal antibody
- Binds human TNF-α (proinflammatory cytokine)
- Early administration (< 10 d) following severe ADE may aid in more complete resolution
- Risk of liver failure



- Abu-Sbeih, H., et al. Early Introduction of Selective Immunosuppressive Therapy Associated with Favorable Clinical Outcomes in Patients with Immune Checkpoint Inhibitor-Induced Colitis. *J Immunother Cancer* 2019: 7(1): 93-104
- Remicade [package insert]. Horsham, PA: Janssen Biotech, Inc; 2018

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Other Agents

- Vedolizumab (Entyvio®)
  - Gut-targeted α4β7 integrin antibody approved for inflammatory bowel disease
  - Prevents immune cell interaction with gut tissue
  - Selective GI tract immunosuppression
- Azathioprine (Imuran®)
  - Prevents purine synthesis and decreases production of B cells
  - Promotes T cell antigen tolerance
  - Induces T cell apoptosis
- Mycophenolate (Cellcept®)
  - Blocks guanine synthesis and decreases production of T cells and B cells

- Abu-Sbeih, H., et al. Outcomes of Vedolizumab Therapy in Patients with Immune Checkpoint Inhibitor–Induced Colitis: A Multi-Center Study. *J Immunotherapy Cancer* 2018: 6(1): 142-153
- Cellcept [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019.
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- Imuran [package insert]. Roswell, GA: Sebela Pharmaceuticals, Inc; 2018.

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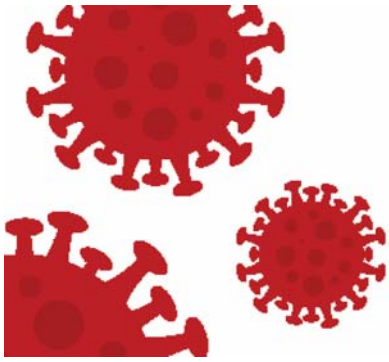
Immunotherapy and SARS-CoV-2



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Immunotherapy and SARS-CoV-2

- WHO pandemic March 11, 2020
- Possible severe, immune-mediated reaction
  - Acute respiratory distress syndrome resulting from cytokine storm
- Pneumonitis possible immunotherapy-related ADE
- Cancer patients at increased risk of severe infection
- No clear evidence of protection with PD-1 pathway uninhibited
- Take proper precautions

PD-1 = Programmed Death-1

- Wu, C., et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; March 13: [Epub ahead of print]

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Key Takeaways

- Immune checkpoints are potent regulators of immune response and can be manipulated by cancer cells to evade tumor specific host defenses.
- Removal of checkpoint blockade, with available anti-PD-1 agents, restores normal immune function and cancer destruction by T cells.
- Treatment with ICPi is often more tolerable than traditional chemotherapy and may lead to durable responses.
- Combining ICPi with other treatment modalities, such as chemotherapy or oral targeted agents, is a successful strategy to increase patient response.
- Adverse events of immune checkpoint blockade are immune-mediated and treated with high dose steroids or other immunosuppressive agents.

PD-1 = Programmed Death-1
ICPi = Immune Checkpoint inhibitor

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Thank You

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Activity Test

The What, Why, and How of Anti-PD-1/PD-L1 Immunotherapy for Cancer

Activity tests must be completed online at www.freeCE.com.
A passing grade of 70 or higher and completion of an online activity evaluation are required to earn credit.

1. All the following are functions of T cells in the recognition and eradication of cancer from the human body EXCEPT:
    a. Migration to the tumor cells
    b. Antigen presentation to other immune cells
    c. Expansion of directed immune cells
    d. Tumor cell lysing by the immune cell

2. Which of the following is a common adverse event associated with immune checkpoint inhibitor therapy?
    a. Febrile neutropenia
    b. Nausea and vomiting
    c. Mucositis
    d. Dermatitis

3. All the following are FDA approved indications for immune checkpoint inhibitor therapy except:
    a. Melanoma
    b. Non-small cell lung cancer
    c. Prostate cancer
    d. Urothelial carcinoma

4. Why is chemotherapy added to immune checkpoint inhibition in the treatment of some cancers?
    a. To decrease immune-mediated adverse events
    b. To increase antigen release from the tumor
    c. To decrease the cost associated with treatment administration
    d. To increase the time interval between treatment administration

5. JT is an 84-year-old male with metastatic non-small cell lung cancer originally diagnosed in March 2020. He has pre-existing comorbidities including hypertension, diabetes, COPD, and degenerative disc disease. He has borderline performance status and his doctor does not think that he will be able to tolerate traditional chemotherapy. Molecular studies were performed on biopsy tissue and show that patient does not have a targetable mutation that would indicate the use of an oral agent for treatment. He was found to have high PD-L1 overexpression and is being started on treatment with pembrolizumab at 400 mg IV given every 6 weeks.

    What is the importance of increased PD-L1 expression by a patient's tumor with respect to treatment benefit with an immune checkpoint inhibitor?
    a. PD-L1 overexpression leads to dampened immune response and increased response to immune checkpoint blockade therapy
    b. PD-L1 overexpression increases tumor specific immune response and increased response to immune checkpoint blockade therapy
    c. PD-L1 overexpression leads to decreased risk of immune-mediated adverse events during treatment with an immune checkpoint inhibitor
    d. PD-L1 overexpression activates B cells and dendritic cells

6. What types of cells are antigen presenting cells?
    a. Dendritic cells
    b. Plasma cells
    c. Cytokines
    d. T lymphocytes

7. How does immunotherapy work to treat cancer?
    a. Disrupts of DNA duplication to kill cancer cells
    b. Inhibits new blood vessel formation to block cancer cell growth
    c. Increases T cell activation to recognize and kill cancer cells
    d. Decreases cancer cell apoptosis

8. All the following immunotherapy agents work to stimulate the immunity-cancer cycle except:
    a. Cytokine administration
    b. Immune checkpoint inhibition
    c. CAR-T cell therapy
    d. Cancer treatment vaccines

9. Why are immune checkpoints important for normal immune system functioning?
    a. They allow for increased cell destruction
    b. They prevent foreign cell destruction
    c. They mediate response to vaccines
    d. They help prevent autoimmunity

10. Which agent is a programmed death -1 pathway inhibitor approved by the FDA for the treatment of cancer?
    a. carboplatin
    b. sipuleucel-T
    c. atezolizumab
    d. ipilimumab

11. What is a risk associated with non-specific activation of the immune system cascade?
    a. Cytokine storm
    b. Alopecia
    c. Cutaneous toxicity
    d. Diabetes

12. CR is a 57-year-old female with metastatic melanoma to the brain. She was originally diagnosed in April of 2017 with localized disease that was treated with surgical resection. She experienced disease recurrence at her surgical scar in April of 2020 and received immunotherapy treatment with ipilimumab. Her treatment course was complicated by Grade 3 colitis (> 7 stools above baseline) that necessitated a drug holiday.

    What is the treatment of choice for the front-line treatment of this immune-mediated ADE?

    a. Loperamide 2-4 mg after each loose stool
    b. Prednisone 0.5 mg/kg for 7 days
    c. Prednisone 1-2 mg/kg daily
    d. Infliximab 5 mg/kg x 3 doses

13. [Please refer to case study listed in previous question.] Patient has been on this front-line treatment for 7 days without any reduction in colitis symptoms. What is a second line treatment that may be beneficial for CR?

    a. Loperamide 2-4 mg after each loose stool
    b. Prednisone 0.5 mg/kg for 7 days
    c. Prednisone 1-2 mg/kg daily
    d. Infliximab 5 mg/kg x 3 doses

14. How do steroids work to dampen an immune response?

    a. Increases expansion of tumor directed T cells
    b. Increases vasodilation and capillary permeability
    c. Decreases vasodilation and capillary permeability
    d. Decreases immune cell apoptosis

15. Which one of these agents has shown efficacy in steroid refractory immune mediated adverse events?

    a. Azathioprine
    b. Loperamide
    c. Magic mouthwash
    d. Granulocyte-colony stimulating factor