Adverse Effects of Immune Checkpoint Inhibitor (ICI) Immunotherapy

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Antineoplastic Immunotherapy

Immunotherapy boosts the body's own immune systems to treat cancer, using immune cells to locate, target and attack cancer cells.

- Cancer vaccines
  - Example: HPV vaccine
- Immune system modulators
  - Example: interleukins, interferons
- Immune effector cell therapy
  - Example: CAR-T cell therapy
- Immune checkpoint inhibitor therapy
  - Example: PD-1/PD-L1 inhibitors

Immune Checkpoint Inhibitor (ICI) Therapy

- Immune Checkpoint Inhibitor (ICI) therapy has been in use since 2011
- A 2020 paper estimated that 36% of cancer patients (~ 234,000 people/year) are eligible for ICI therapy
- The number of active clinical trials studying ICIs is over 3,000 to date
- Use is rapidly expanding with multiple ICI drugs currently available to treat over 80 FDA approved cancer indications
- ICI therapy is now being used in earlier stages of cancer and as a first-line treatment, increasingly as the standard of care for many types of cancer

Haslam, JAMA Netw Open, 2020
Tang, Nat Rev Drug Disc, 2018

FDA Approvals for ICI Therapy

2011
- March 25, 2011 — Ipi for unresectable or metastatic melanoma

2014
- September 4, 2014 — Pembro for unresectable or metastatic melanoma
- December 23,2014 — Nivo for unresectable or metastatic melanoma

Immune Checkpoint Inhibitors

- **Anti PD-1**
  - Cemiplimab
  - Dostarlimab
  - Nivolumab
  - Pembrolizumab
  - Retifanlimab
- **Anti PD-L1**
  - Atezolizumab
  - Avelumab
  - Durvalumab
- **Anti CTLA-4**
  - Ipilimumab
  - Tremelimumab
- **Anti LAG-3**
  - Relatlimab

2015
- October 1, 2015 — Nivo + Ipi for melanoma (BRAF V600 wild-type)
- October 2, 2015 — Pembro for NSCLC
- October 9, 2015 — Nivo for second line NSCLC
- October 29, 2015 — Ipi for melanoma with complete resection
- November 13, 2015 — Nivo for second line squamous NSCLC
- November 23, 2015 — Nivo for RCC
- December 18, 2015 — Pembro for unresectable melanoma

2016
- May 16, 2016 — Nivo for cHL
- May 17, 2016 — Atezo for urothelial carcinoma
- August 4, 2016 — Pembro for SCCHN
- October 17, 2016 — Atezo for NSCLC
- October 23, 2016 — Pembro for first line NSCLC
- November 9, 2016 — Nivo for SCCHN

2017
- February 1, 2017 — Nivo for urothelial carcinoma
- March 14, 2017 — Pembro for cHL
- March 22, 2017 — Avelu for MCC
- April 30, 2017 — Durva for urothelial carcinoma
- May 8, 2017 — Avelu for urothelial carcinoma
- May 9, 2017 — Pembro for non-squamous NSCLC
- May 17, 2017 — Pembro for urothelial carcinoma
- May 22, 2017 — Pembro for colorectal cancer and other solid tumor
- August 1, 2017 — Nivo for colorectal cancer
- September 22, 2017 — Pembro for gastric cancer
- December 20, 2017 — Nivo for metastatic melanoma with complete resection

2018
- February 16, 2018 — Durva for unresectable NSCLC
- April 16, 2018 — Nivo + Ipilumab for RCC
- June 12, 2018 — Pembro for cervical cancer
- June 13, 2018 — Pembro for PMBCL
- July 10, 2018 — Nivo + Ipi for MSI-H
- August 17, 2018 — Nivo for SCLC
- August 20, 2018 — Pembro + Platinum in 1st line, NSCLC
- November 9, 2018 — Pembro in HCC
- December 6, 2018 — Atezo + Beva + Taxol + Carbo for NSq NSCLC
- December 19, 2018 — Pembro in merkel

2019
- February 15, 2019 — Pembro in adjuvant melanoma
- March 8, 2019 — Atezo + Nab-Taxol for TNBC
- March 18, 2019 — Atezo + Carbo/Etop in SCLC
- April 11, 2019 — Pembro for stage 3 NSCLC
- April 19, 2019 — Pembro + Axitinib for RCC
- May 14, 2019 — Avelu + Axitinib for 1st line RCC
- June 10, 2019 — Pembro for metastatic HNSCC
- June 17, 2019 — Pembro for metastatic SCLC
- July 30, 2019 — Pembro for esophageal squamous cell
- September 17, 2019 — Pembro + Lenvatinib for endometrial carcinoma
- September 27, 2019 — Pembro for endometrial carcinoma
- December 3, 2019 — Atezo + Beva + Taxol + Carbo for NSq NSCLC

2020
- January 8, 2020 — Pembro for high - risk bladder cancer
- March 11, 2020 — Nivo + Ipi for HCC
- March 30, 2020 — Durva + Etoposide + Carbo or Cisplatin for ES-SCLC
- May 15, 2020 — Nivo + Ipi for NSCLC
- May 18, 2020 — Atezo for NSCLC
- May 26, 2020 — Nivo + Ipi + Chemo for NSCLC
- May 29, 2020 — Atezo + Beva for untreated HCC
- June 10, 2020 — Nivo for esophageal squamous cell
- June 16, 2020 — Pembro for TMB-H
- June 24, 2020 — Pembro for cutaneous squamous cell carcinoma
- June 29, 2020 — Pembro for colorectal cancer
- June 30, 2020 — Avelu for bladder cancer
- July 30, 2020 — Atezo + Cobimetinib + Vemurafenib in melanoma
- October 2, 2020 — Nivo + Ipi for mesothelioma
- November 13, 2020 — Pembro + Chemo for advanced breast cancer

2021
- January 22, 2021 — Nivo + Chemo for RCC
- February 2, 2021 — Cemi for advanced basal cell carcinoma
- February 22, 2021 — Cemi for NSCLC
- March 22, 2021 — Pembro + Chemo for esophageal carcinoma
- April 16, 2021 — Nivo + Chemo for gastric cancer
- April 22, 2021 — Dostar for endometrial cancer
- May 5, 2021 — Pembro + Chemo for gastric cancer
- May 20, 2021 — Nivo for esophageal
- July 21, 2021 — Pembro + lenvatinib for endometrial cancer
- July 27, 2021 — Pembro for breast cancer
- August 17, 2021 — Dostar for all dMMR tumor
- August 19, 2021 — Nivo for urothelial cancer
- October 13, 2021 — Pembro for cervical cancer
- October 15, 2021 — Atezo for NSCLC
- November 17, 2021 — Pembro for RCC
- December 3, 2021 — Pembro for Stage IIB/IIC Melanoma

2022
- March 4, 2022 — Nivo + Chemo for NSCLC
- March 18, 2022 — Nivo + Relatinib for melanoma
- March 21, 2022 — Pembro for endometrial carcinoma
- May 27, 2022 — Ipi + Nivo for esophageal SCC
- May 27, 2022 — Nivo + Chemo for esophageal SCC
- September 2, 2022 — Durva for bile duct cancer
- October 21, 2022 — Treme + Dirva for HCC
- November 8, 2022 — Cemip + Chemo for NSCLC
- November 10, 2022 — Treme + Durva + Chemo for NSCLC

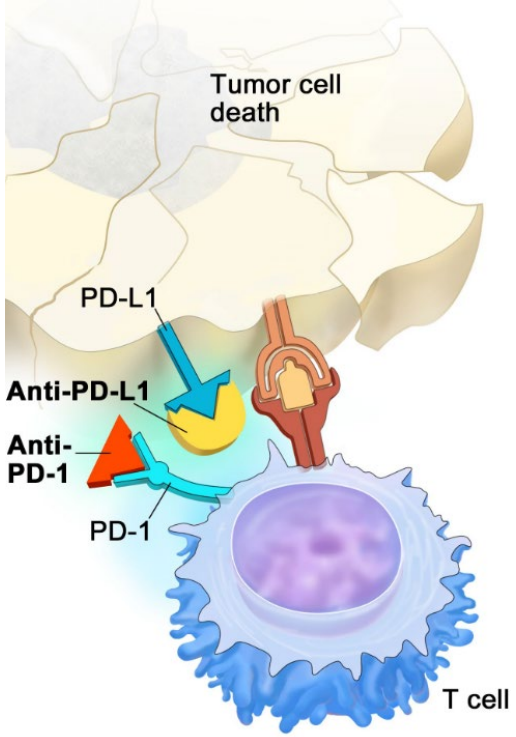
2023
- January 26, 2023 — Pembro for NSCLC
- February 9, 2023 — Dostar for endometrial cancer
- March 22, 2023 — Retifanlimab for Merkel cell carcinoma

How Immune Checkpoint Inhibitors Work

- T-cells are an essential component of the body's immune system, capable of targeting and combating cells that have become cancerous
- T-cells have "checkpoint proteins" on their surface that modulate immune function
- Cancer cells can use signals to evade detection, keeping the immune system inactive against the cancer cells
- ICI therapy literally inhibits these signals, allowing T-cells to properly recognize cancer cells and target them for attack

Designed to activate the immune system to recognize cancer cells

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell



PD= Programmed Death

PD-L = PD ligand

ligands : receptors (keys : locks)

Distinction from Other Cancer Treatments

Immune Checkpoint Inhibitors (ICI) are an entire class of cancer treatment, distinct from other types of cancer treatment.

≠ Immune Effector Cell Therapy

- In CAR-T cell therapy, the patient's own T-cells are harvested, modified, and reinfused
- Immune checkpoint inhibitors are "off-the-shelf" drugs (monoclonal antibodies)

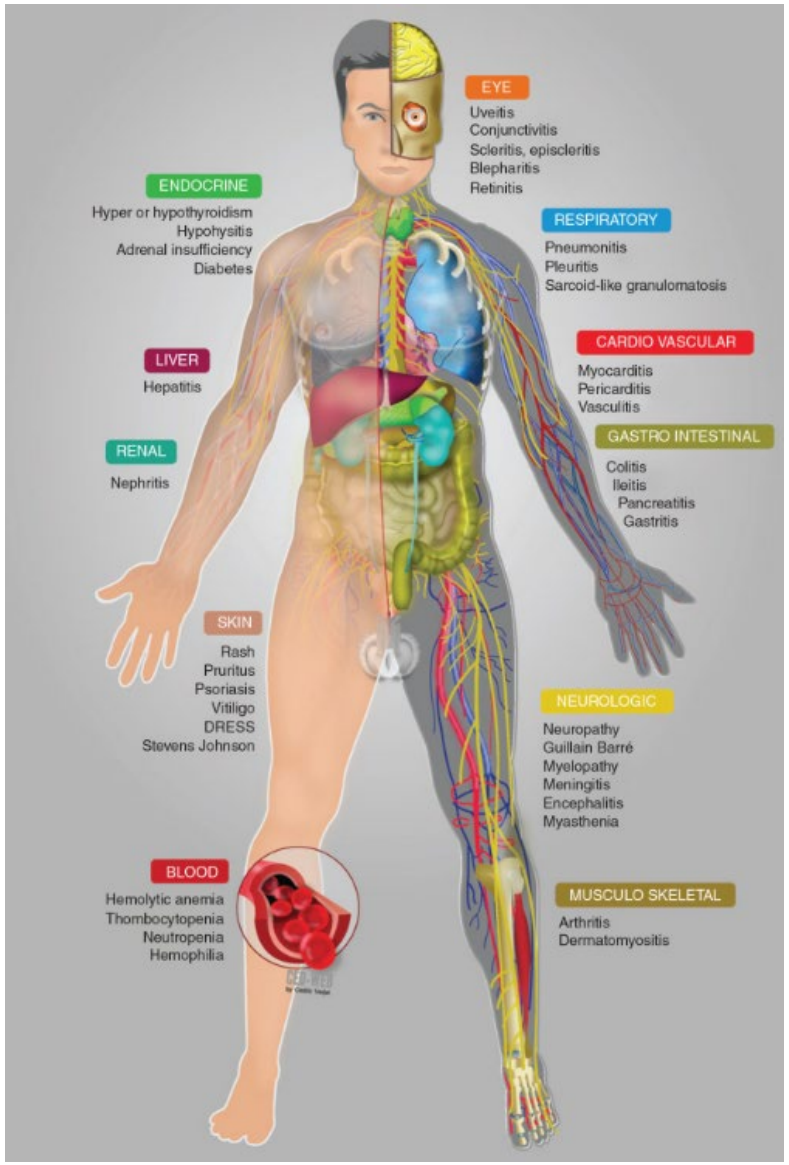
≠ Chemotherapy

- Chemotherapy is cytotoxic and suppresses the immune system
- Immune checkpoint inhibitors have the opposite effect of *activating* the immune system

Immune Related Adverse Events (irAEs)

- Like all drugs, ICI therapy is subject to adverse effects
- Most adverse effects can be managed as outpatient
- About 14-34% of patients have severe adverse effects

When due to ICI, treatment and outcomes for these adverse effects significantly differ from the standard



Examples

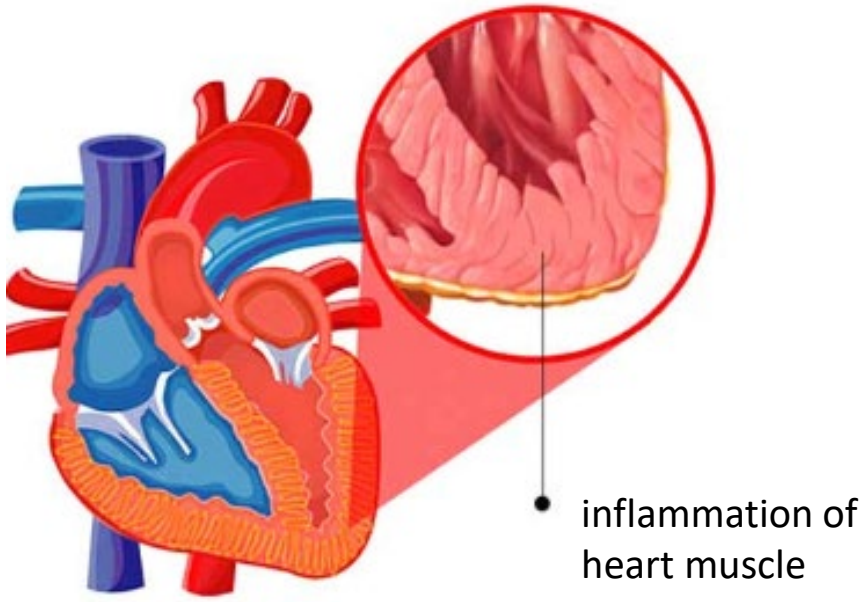
- Colitis
- Hepatitis
- Pneumonitis
- Endocrinopathies
- Myocarditis
- AKI and nephritis
- Arthritis
- Dermatitis
- Neuropathies
- Uveitis

Arnaud-Coffin, IJC, 2019
Wang, JAMA Onc, 2020

Adverse Effect: Treatment of Myocarditis

Standard

- Myocarditis is usually viral
- Standard treatment is reduced activity and surveillance by a cardiologist
- Fatality rate is <8% and risk of major adverse cardiac event is about 6%



ICI-Related Myocarditis

- Treatment is high dose immunosuppression with close and frequent observation
- Fatality rate is 20-50% and risk of major adverse cardiac event is >25%

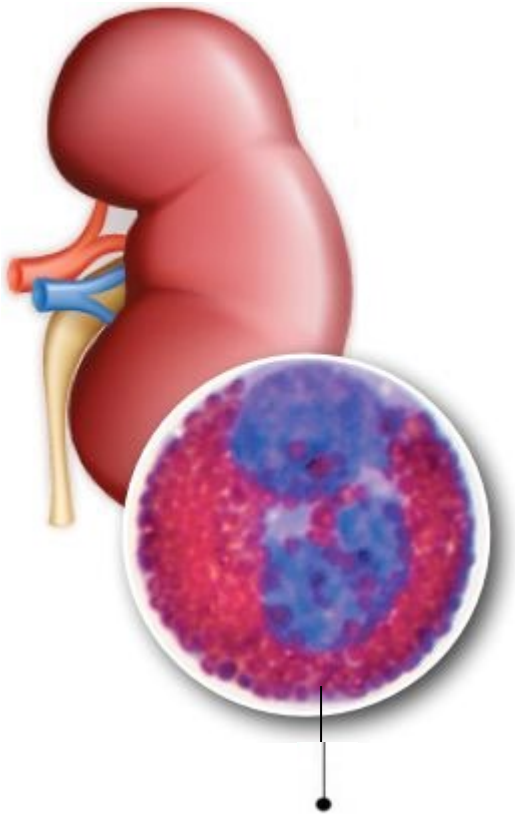
Adverse Effect: Acute Interstitial Nephritis

Standard

- AIN is usually due to hypersensitivity to medication
- Standard treatment is to discontinue the medication with short-term administration of corticosteroids

ICI-Related Acute Interstitial Nephritis

- Diagnosis is challenging because "classic" AIN signs and symptoms are rarely present
- Treatment is high dose immunosuppression with corticosteroids for 6+ weeks
- ICI therapy is held while AIN is being treated and there are then multiple issues in deciding whether to restart



inflammatory infiltrate in kidney interstitium

Timeline for ICI Adverse Effects

- Typically, adverse effects of drugs arise while the patient is actively taking a drug and resolve after the drug is discontinued
- ICI-related adverse effects have the potential for longstanding effects that turn into chronic conditions
- Adverse effects can occur during ICI therapy and also after ICI therapy is completed, sometimes months or even years afterward
  - Example: In one study, ocular adverse effects occurred one year after ICI therapy was discontinued
  - Example: In another study, the maximum time for some adverse effects to appear was as late as three years

Tang, Can Res Treat, 2021
Patrinely, JAMA Onc, 2021

Data Needs

- Continued rapid uptake and expanding use has increased the need for recognition and identification of ICI adverse effects in national databases
- This will enable researchers to clearly track occurrence, define incidence, and inform clinical strategies for management
- In addition, the ability to identify individuals who are status post ICI therapy in longitudinal data will enable monitoring of delayed adverse effects

Questions?

Project Data Sphere®

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