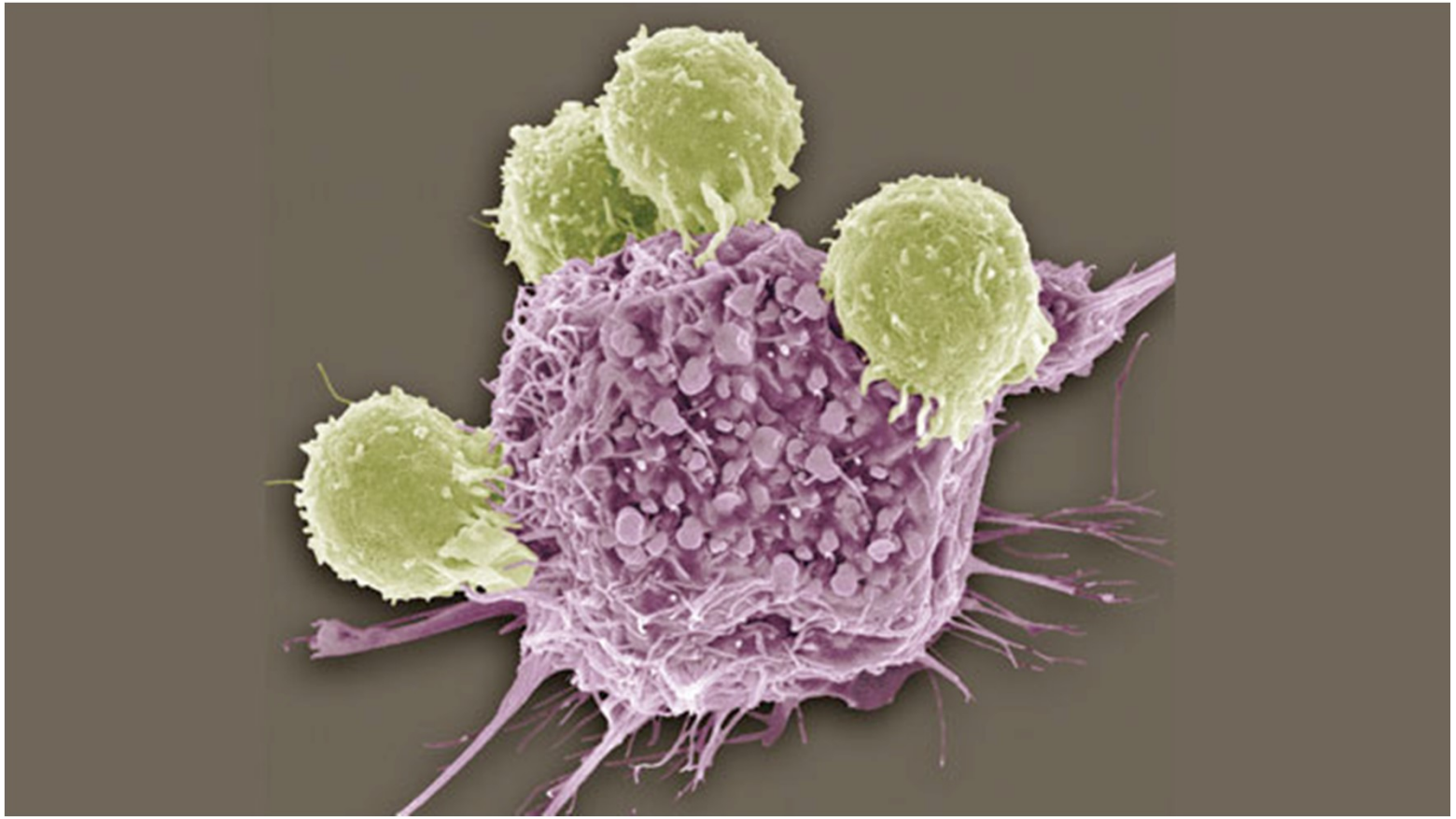
MultiCare Regional Cancer Center
BetterConnected

CANCER IMMUNOTHERAPY 2018

Presented by John A Keech Jr DO

MultiCare Regional Cancer Center

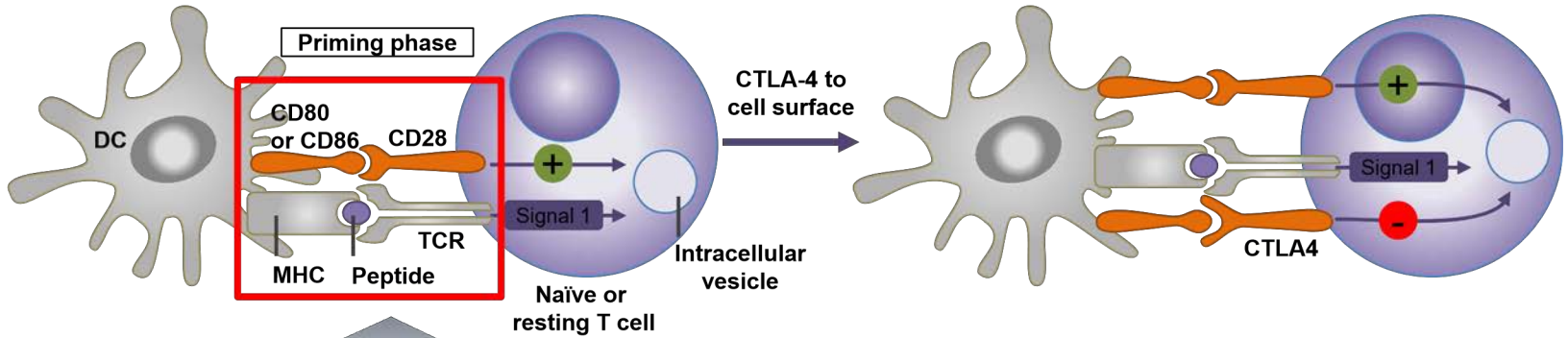
Successful anti-cancer immunity is autoimmunity

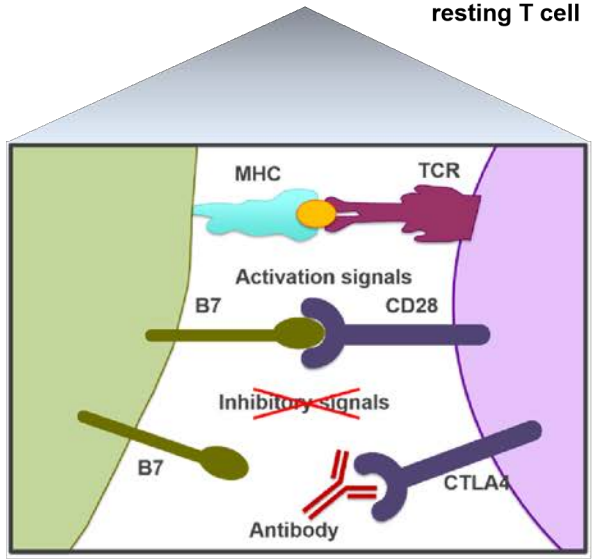


Green, The Scientist, 2014

Immunotherapy strategies

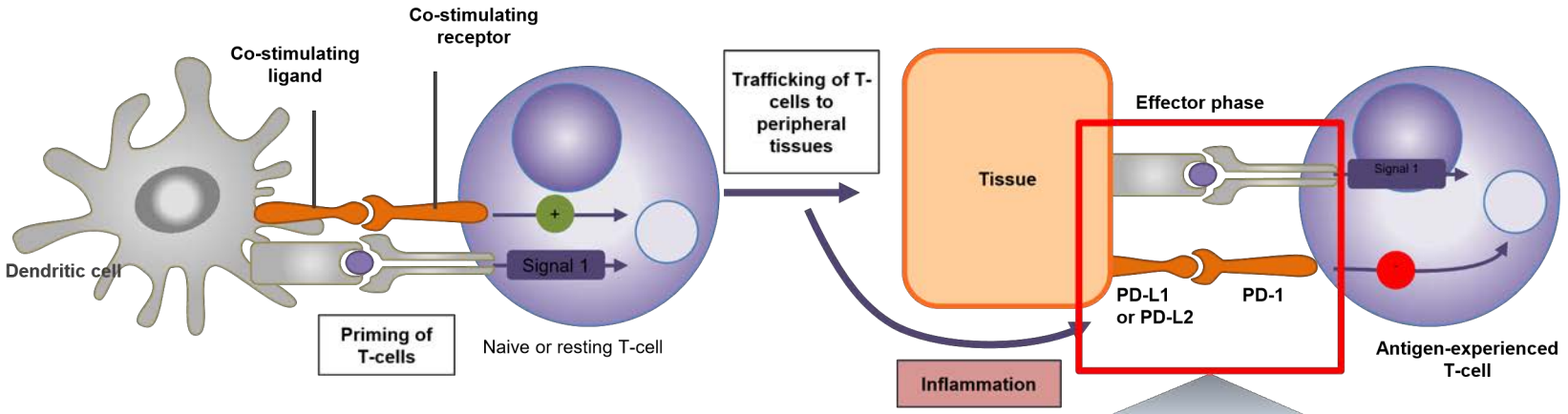
- Cancer vaccines
- Cytokines
- Adoptive T cell therapy
- Checkpoint inhibitors



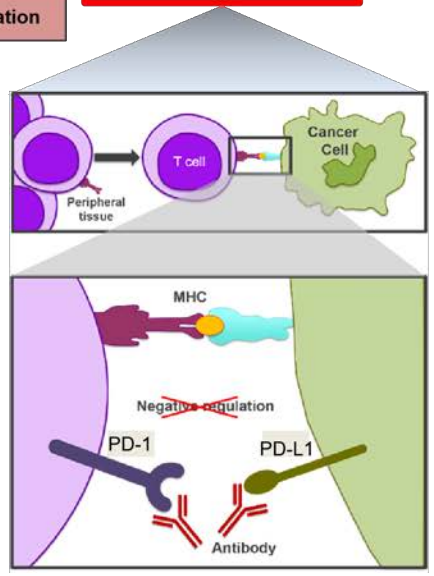


Pardoll, Nat Rev Ca, 2012; Ribas et al, NEJM, 2012

- Impacts T-cell priming
- Occurs during initial interaction of T-cells with APC
- Blocks activation in the lymph nodes
- Regulates amplitude of early activation of naïve and memory T-cells
- Antibodies targeting CTLA-4
- High toxicity, little response as single agent in gynecologic cancers (OvCa)



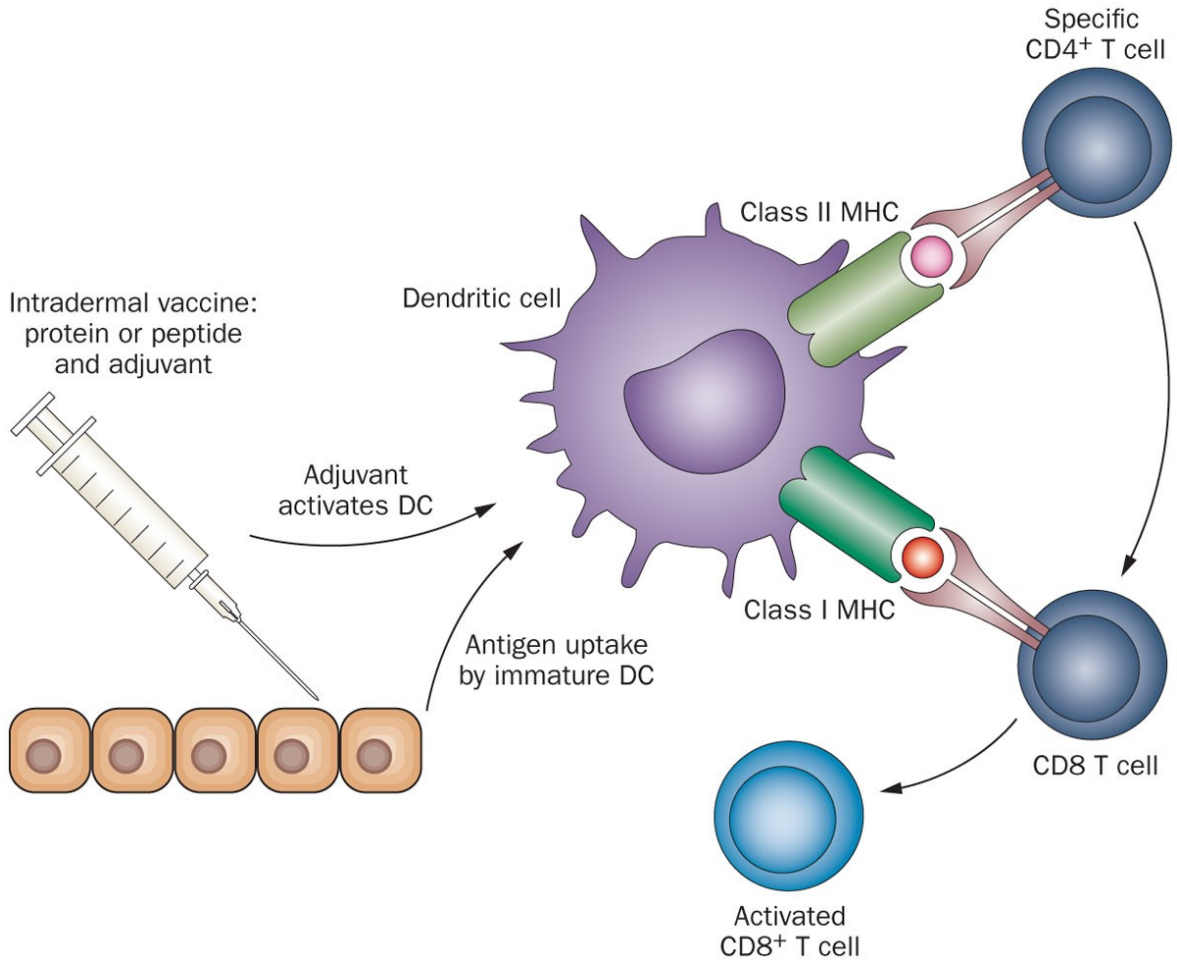
- Impacts activation during inflammation
- Prevents T-cell expansion
- Blocks activation in the peripheral tissue
- Mechanism that limits autoimmunity
- More broadly expressed than CTLA-4



FDA approved indications for checkpoint inhibitors

Year	Agent	Target	Indication
2011	Ipilimumab	CTLA-4	Melanoma
2014	Nivolumab Pembrolizumab	PD-1 PD-1	Melanoma
2015	Nivolumab Pembrolizumab	PD-1 PD-1	NSCLC
2015	Nivolumab	PD-1	RCC
2015	Nivolumab+ Ipilimumab	PD-1+ CTLA-4	Melanoma
2015	Pembrolizumab	PD-1	Head Neck SCC
2016	Nivolumab	PD-1	Hodgkin lymphoma
2016	Atezolizumab	PD-L1	Urothelial cancer
2017	Avelumab	PD-L1	Merkel cell carcinoma
2017	Durvalumab	PD-L1	Urothelial cancer

Mechanism of action of cancer vaccines



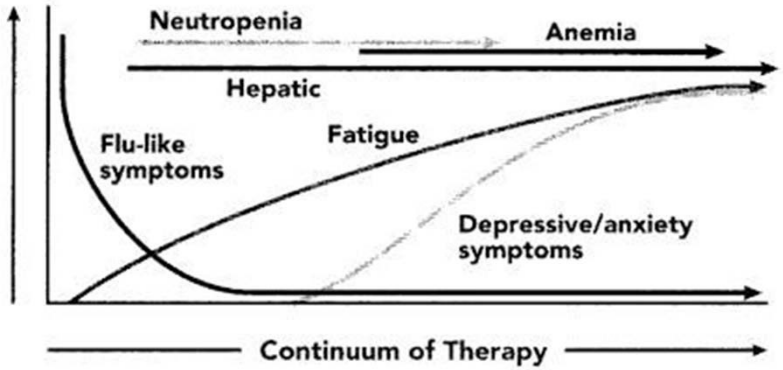
Drake (2013) Nat. Rev. Clin. Oncol.

Vaccine toxicities

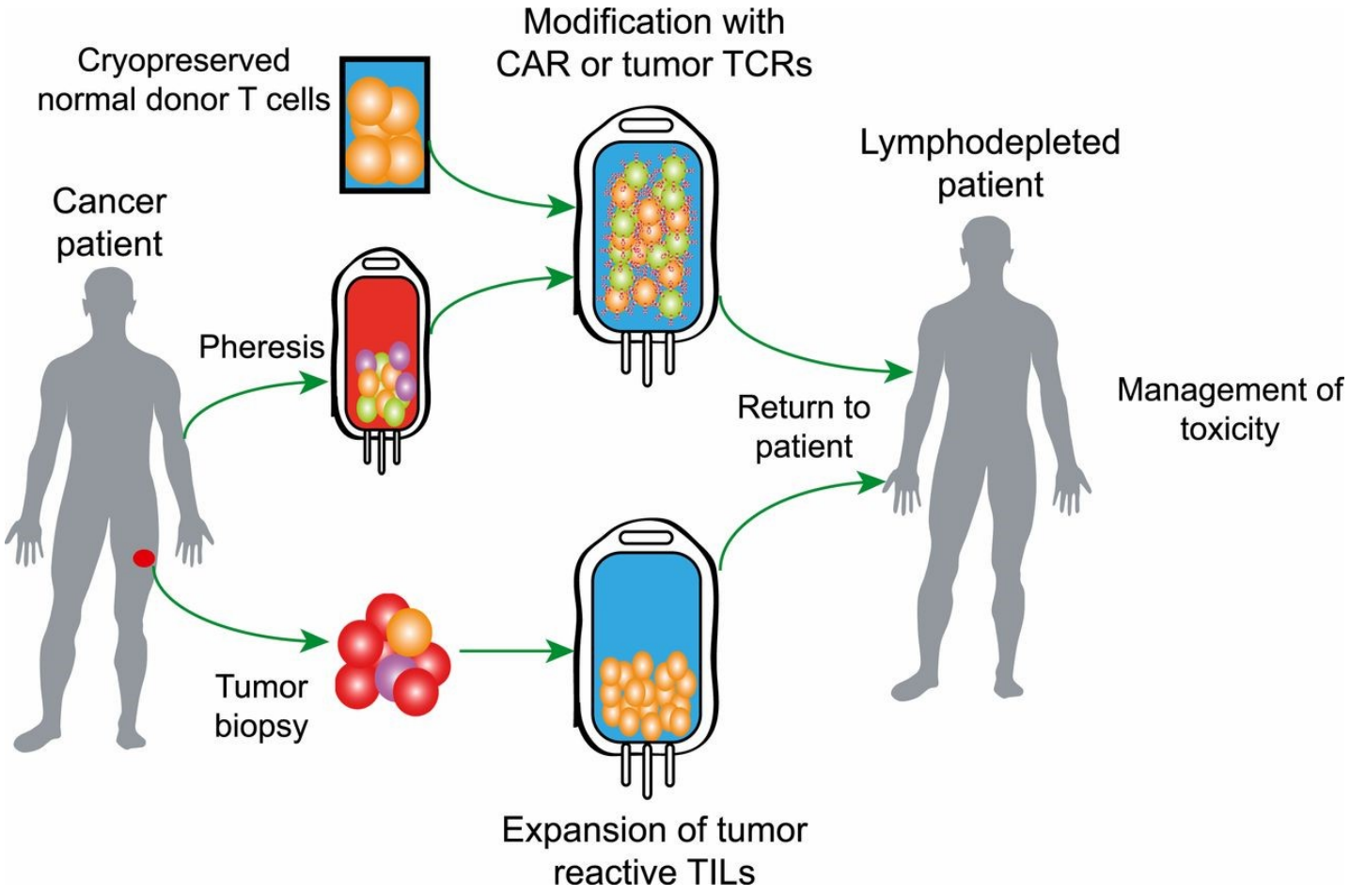
- General
  - Fever, chills, lethargy
- Dermatologic
  - Maculopapular rash, vitiligo
- Gastrointestinal
  - Diarrhea
- Liver
  - Elevated LFTs
- Endocrine
  - None
- Other
  - Local reactions, back pain, hypotension

Cytokine toxicities

- General
  - Fever, chills, lethargy, flu-like symptoms
- Dermatologic
  - Maculopapular rash, petechial
- Gastrointestinal
  - Diarrhea, nausea, vomiting
- Liver
  - Elevated LFTs
- Endocrine
  - Thyroiditis
- Other
  - CHF, pulmonary edema, hypotension, thrombocytopenia, leukopenia, mental status changes



Adoptive T cell therapy



Barrett et al. J Immunol 2015

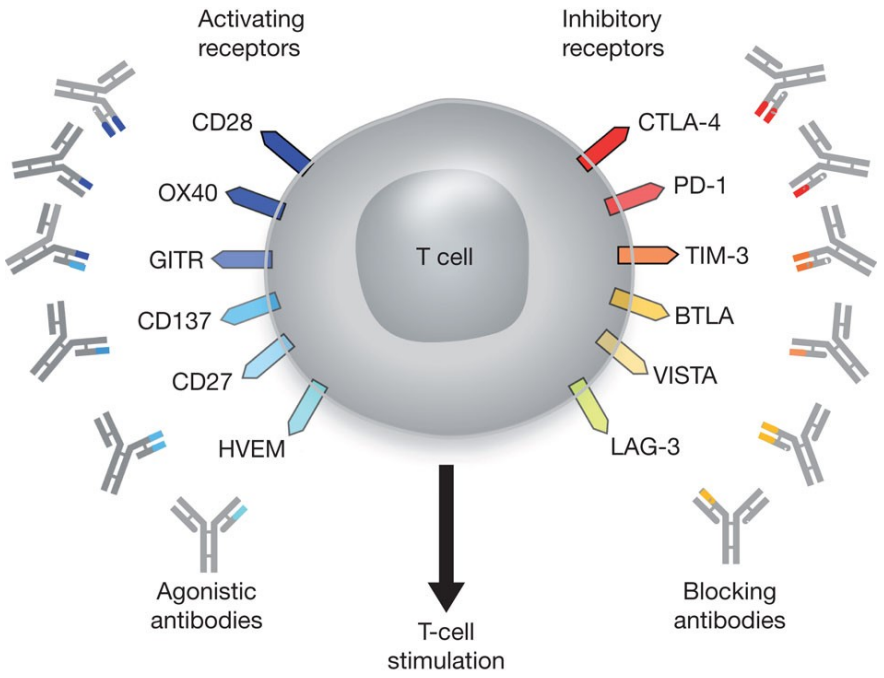
Adoptive T cell toxicities

- General
  - Fever, chills, lethargy, fatigue
- Dermatologic
  - Maculopapular rash, vitiligo
- Gastrointestinal
  - Diarrhea, colitis
- Liver
  - Elevated LFTs
- Endocrine
  - Thyroiditis
- Other
  - Lymphopenia, CMV, tachycardia, hypotension, oliguria, pulmonary edema, encephalopathy, carditis

CAR-T CELL INFUSION TOXICITY MEDIATED THROUGH CYTOKINE STORM: IL-6

- AT THE PRESENT TIME, ADMINISTRATION IN A MONITORED ICU SETTING
- IL-6 INHIBITORS: TOCLIZUMAB AND SARILUMAB

T cell targets for antibody therapy



Mellman, Nature (2011)

Checkpoint inhibitor toxicities

- General
  - Fever, chills, lethargy, fatigue
- Dermatologic
  - Maculopapular rash, vitiligo
- Gastrointestinal
  - Diarrhea, colitis
- Liver
  - Elevated LFTs
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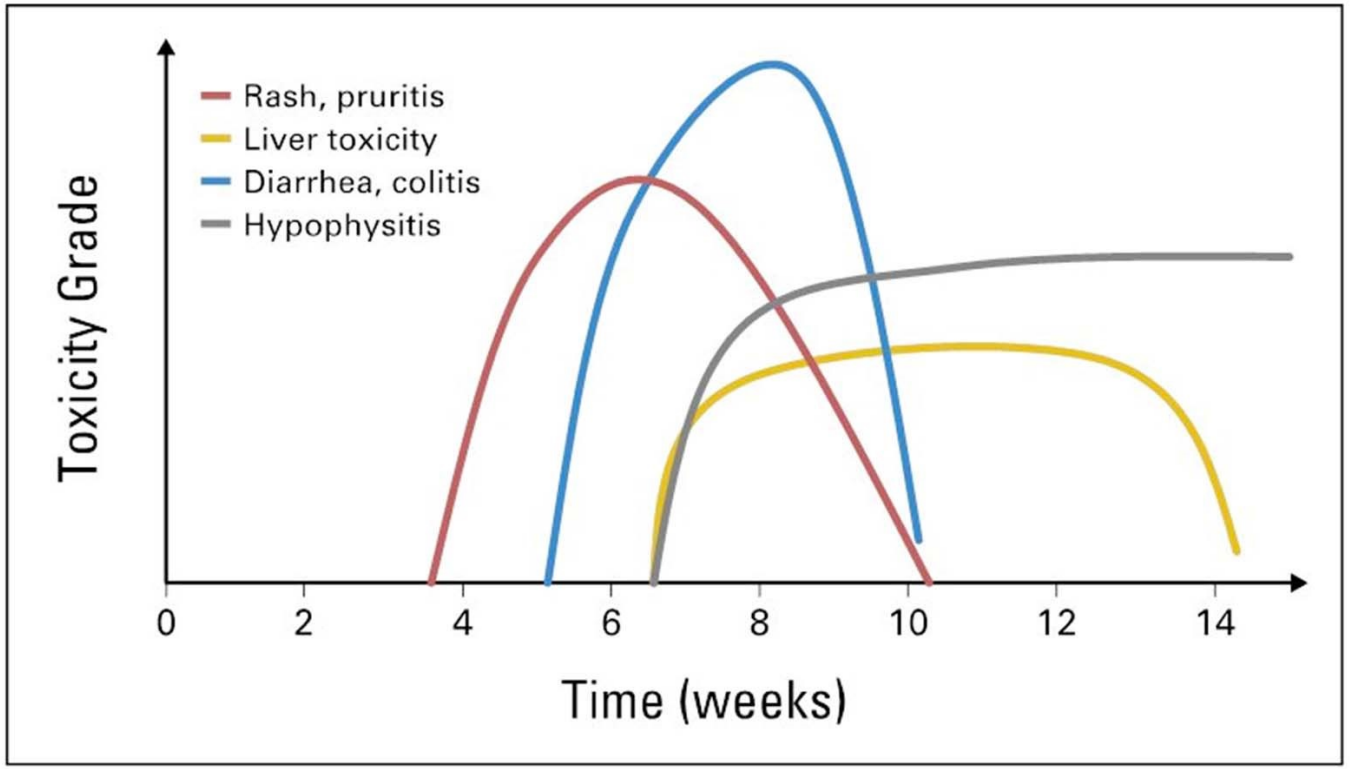
Kinetics of immune related adverse events with ipilimumab

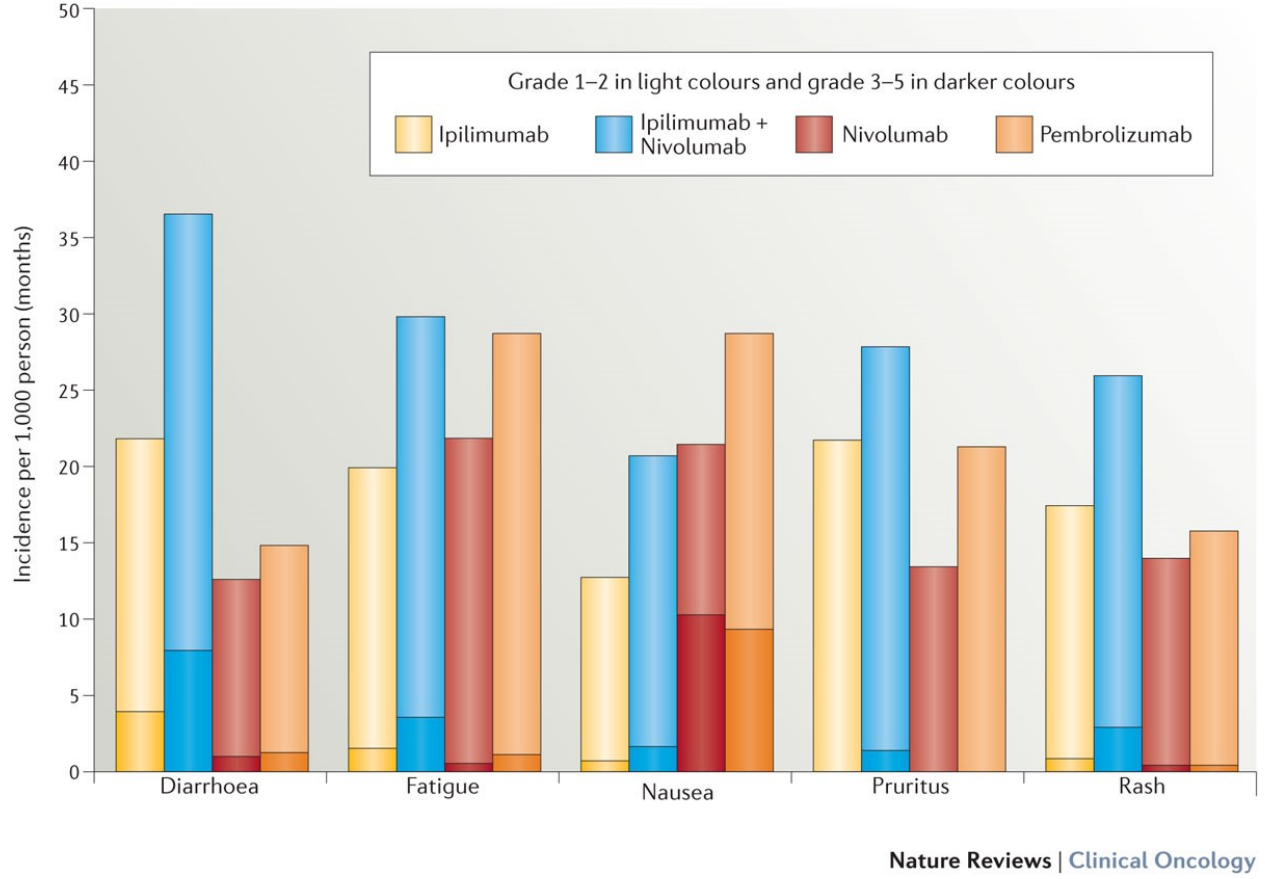


Weber, JCO 2012

Immune-mediated adverse reactions for nivolumab (n=1994)

	All Grades n (%)	Median time to onset, months (range)
Pneumonitis*	61 (3.1%)	3.5 (1 day to 22.3 months)
Colitis	58 (2.9%)	5.3 (2 days to 20.9 months)
Hepatitis	35 (1.8%)	3.3 (6 days to 9 months)
Hypophysitis	12 (0.6%)	4.9 (1.4 months to 11 months)
Adrenal insufficiency	20 (1.0%)	4.3 (15 days to 21 months)
Hypothyroidism/thyroiditis	171 (9.0%)	2.9 (1 day to 16.6 months)
Hyperthyroidism	54 (2.7%)	1.5 (1 day to 14.2 months)
Diabetes	17 (0.9%)	4.4 (15 days to 22 months)
Nephritis/renal dysfunction	23 (1.2%)	4.6 (23 days to 12.3 months)
Skin*	171 (9.0%)	2.8 (<1 day to 25.8 months)
Encephalitis	3 (0.2%)	-

Most common adverse events with anti-CTLA-4 and anti-PD-1



Boutros (2016) Nat. Rev. Clin. Oncol.

Infusion Related Reactions

- Stop infusion
- Give IV:
  - Diphenhydramine 50 mg
  - Ranitidine 50 mg
- Med choice by symptom:
  - Fever, chills, headache, diaphoresis
    - Acetaminophen, ibuprofen or naproxen
  - Rigors
    - IV meperidine 50 mg-can be given every 5 minutes times 3
- If does not resolve in 30 minutes or worsens
  - Consider IV steroids or epinephrine
- After symptom resolution, restart infusion at 50% infusion rate

General guidelines

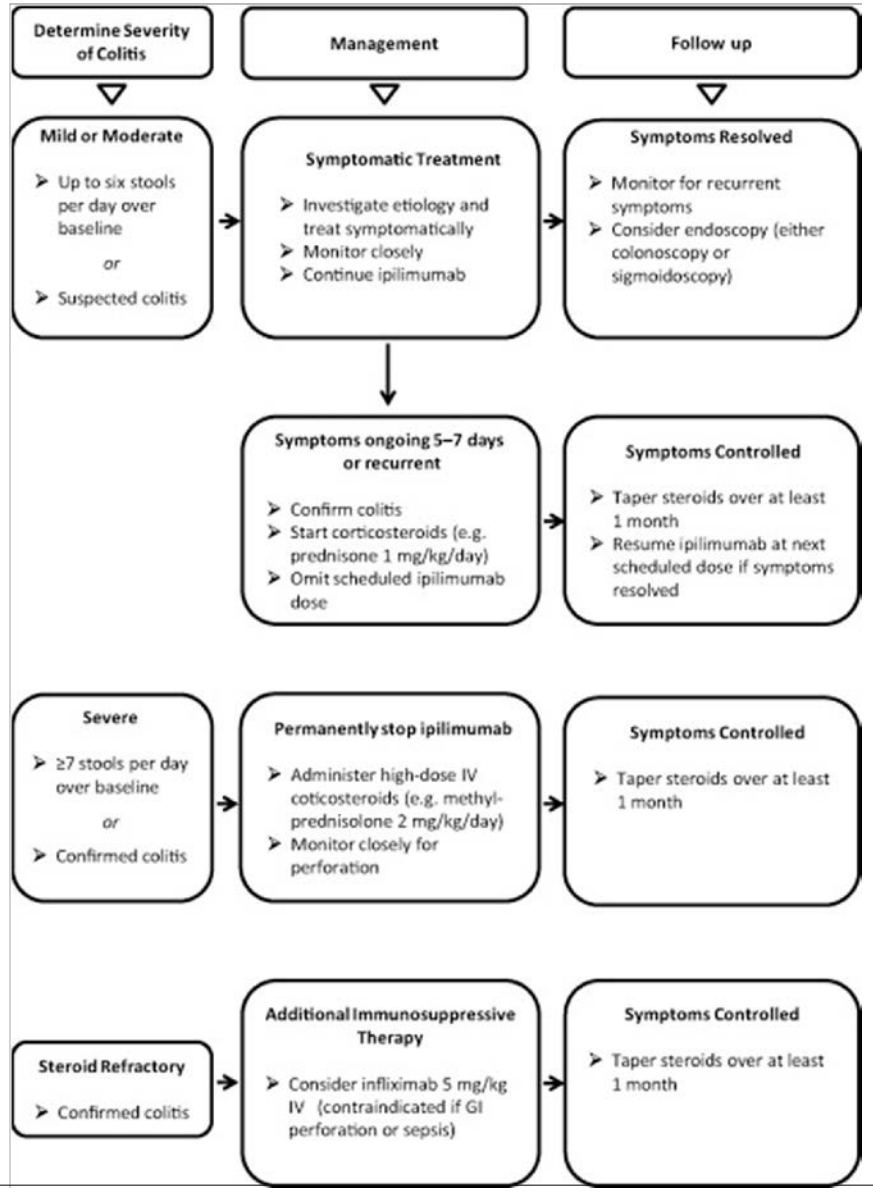
- Low grade (1-2) toxicities
  - Observe
  - Hold drug
  - Topical steroids
- Medium grade (2-3) toxicities
  - Hold drug
  - Oral systemic steroids
  - Closer monitoring
- High grade (3-4) toxicities
  - Admit
  - IV steroids
- Steroid-refractory toxicities
  - Other immunosuppressive agents

Management of grade 3 and 4 events

Type and Severity of irAE	Initial Management	Additional Immunosuppression	Immunosuppression Tapering Schedule
Colitis and/or diarrhea Grade 3-4 • Increase of ≥7 stools per day over baseline • Abdominal pain, fever, and change in bowel habits	• Admit to hospital for intravenous corticosteroid therapy (methylprednisolone 1-2 mg/kg daily dose) • Supportive care including intravenous fluids, supplemental oxygen, and antibiotics as needed • Withhold hepatotoxic drugs • Consider further diagnostic imaging or procedures	**Colitis and/or diarrhea** • If no improvement after 3 days, give infliximab 5 mg/kg • Can redose infliximab after 2 weeks if needed	**Colitis and/or diarrhea** • Rapidly tapering course of steroids as tolerated over 4-6 weeks • Increase steroids if diarrhea flares and then restart tapering
Hepatitis Grade 3-4 • Aspartate transaminase and/or alanine transaminase levels >5 times ULN • Total bilirubin level >3 times ULN		**Hepatitis** • If no improvement after 3 days, start mycophenolate mofetil 500-1000 mg every 12 hours	**Hepatitis** • Rapidly tapering course of steroids as tolerated; discontinue mycophenolate mofetil once tapered to prednisone 10 mg daily
Pneumonitis Grade 3-4 • Severe, life-threatening symptoms • Worsening hypoxia		**Pneumonitis** • If no improvement after 48 hours, start additional agent as above or cyclophosphamide	**Pneumonitis** • Taper steroids slowly over 6 weeks • Mycophenolate mofetil management as above if needed

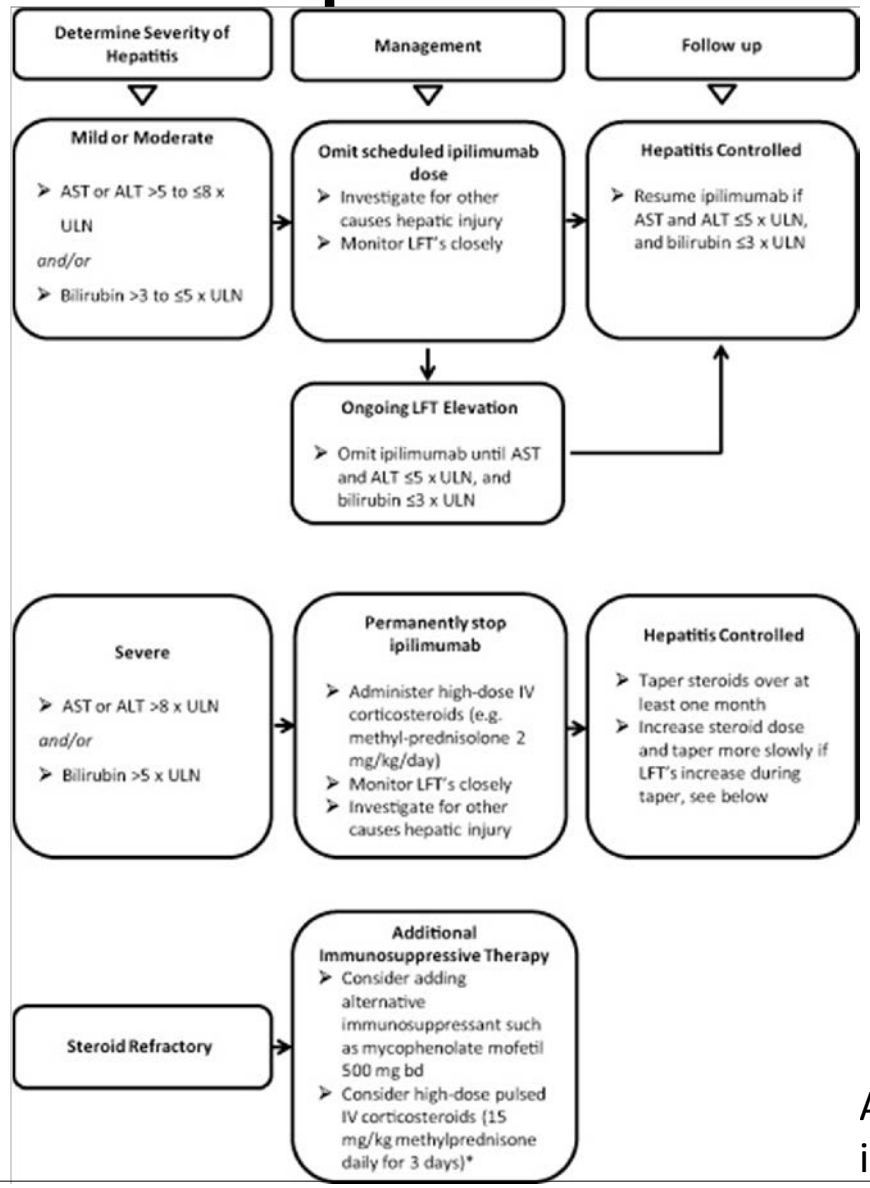
Friedman, JAMA Oncology 2016

Management of colitis

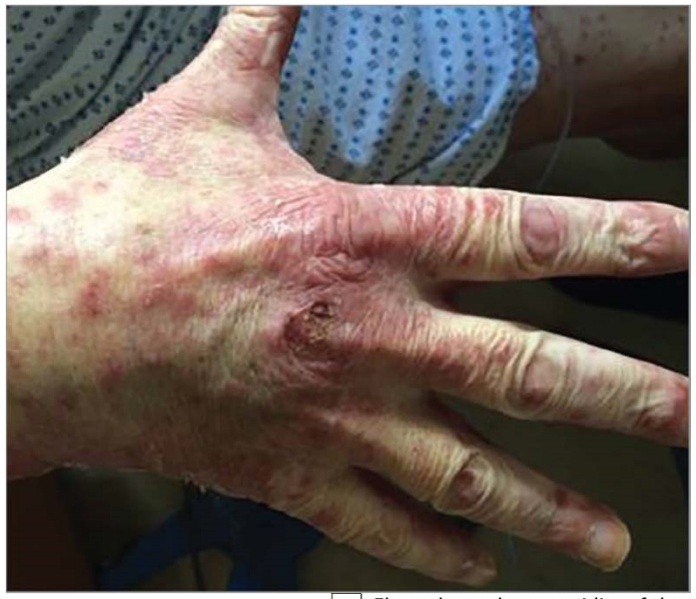


Adapted from the YERVOY irAR Management Guide

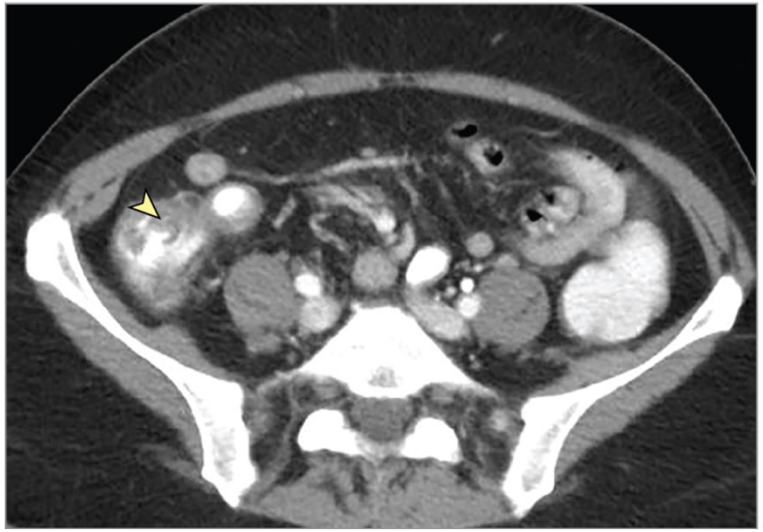
Management of hepatitis



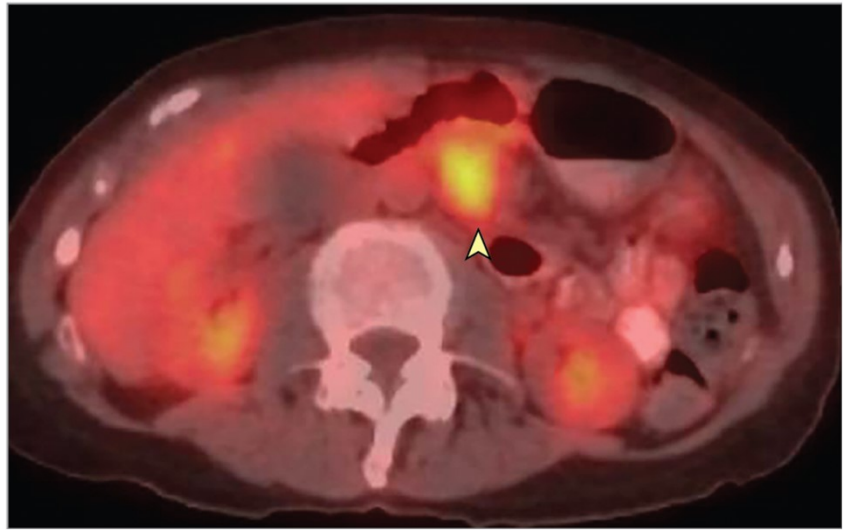
Adapted from the YERVOY irAR Management Guide



A Mural thickening of the ascending colon

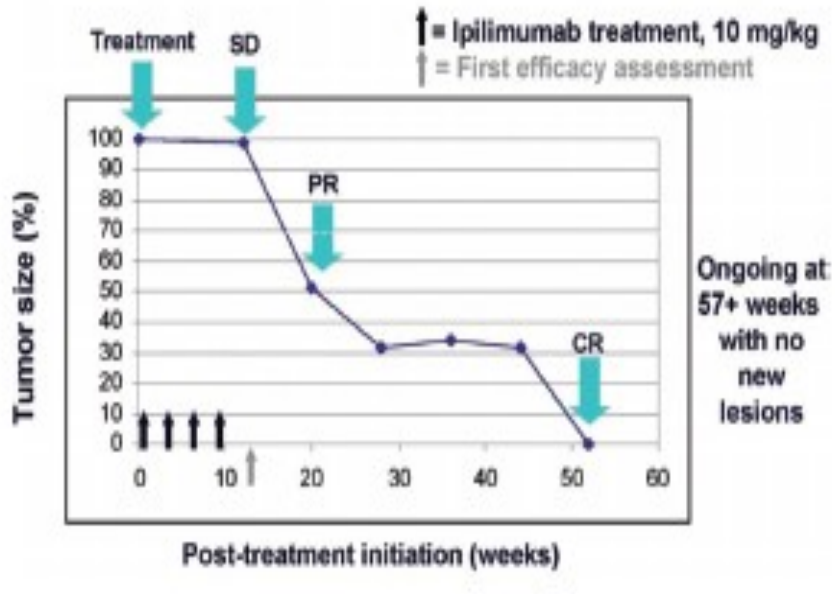


B Fluorodeoxyglucose avidity of the pancreas



Friedman, JAMA Oncology 2016

T cells continue to evolve even after drug is cleared



Responses as late as 106 weeks

- When toxicities occur is variable
- Early and late
- Prolonged treatment
- May need to treat again

Weber, Oncologist, 2008

Summary

- Prompt recognition of unique immune related toxicities
- Grade severity
- Toxicities may persist and elaborate even after stopping drug
- Consult subspecialty services
  - Pulmonary, endocrinology, dermatology, GI, etc.
- With more FDA indications--very rare side effects
- Immune combinations may lead to higher rates of adverse events