Cancer immunotherapy: successes and pitfalls for the non-oncologist

Daniel W. Bowles, MD
Associate Professor of Medicine
Program Director, Hematology/Oncology Fellowship
University of Colorado
daniel.bowles@cuanschutz.edu

Conflicts of interest

- DSMB for BioMetrix

Learning objectives

- Recognize basic immunotherapy and biology and its impact on cancer therapy
- Diagnose and treat immunotherapy side effects
- Identify which cancers are best suited for immunotherapy

FACT OF THE DAY

"[After immunotherapy] ... they didn't find any cancer at all."

– **JIMMY CARTER**
Former U.S. President

CANCER RESEARCH INSTITUTE

Cancerresearch.org

Cancer immunotherapy wins Nobel Prize

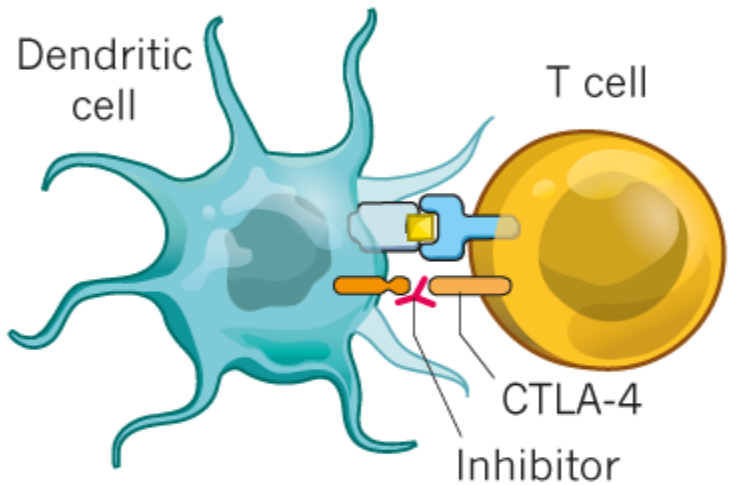
James P. Allison

Tasuku Honjo

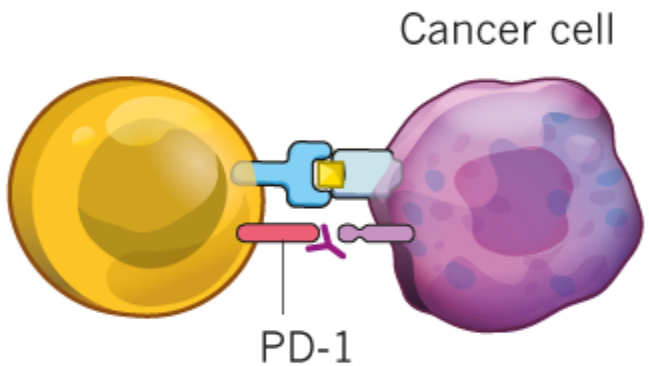
Nature.com

CHECKPOINT INHIBITOR DRUGS

'Checkpoint' proteins block T-cell activity. Inhibitor drugs can release the brakes on T cells at different stages.

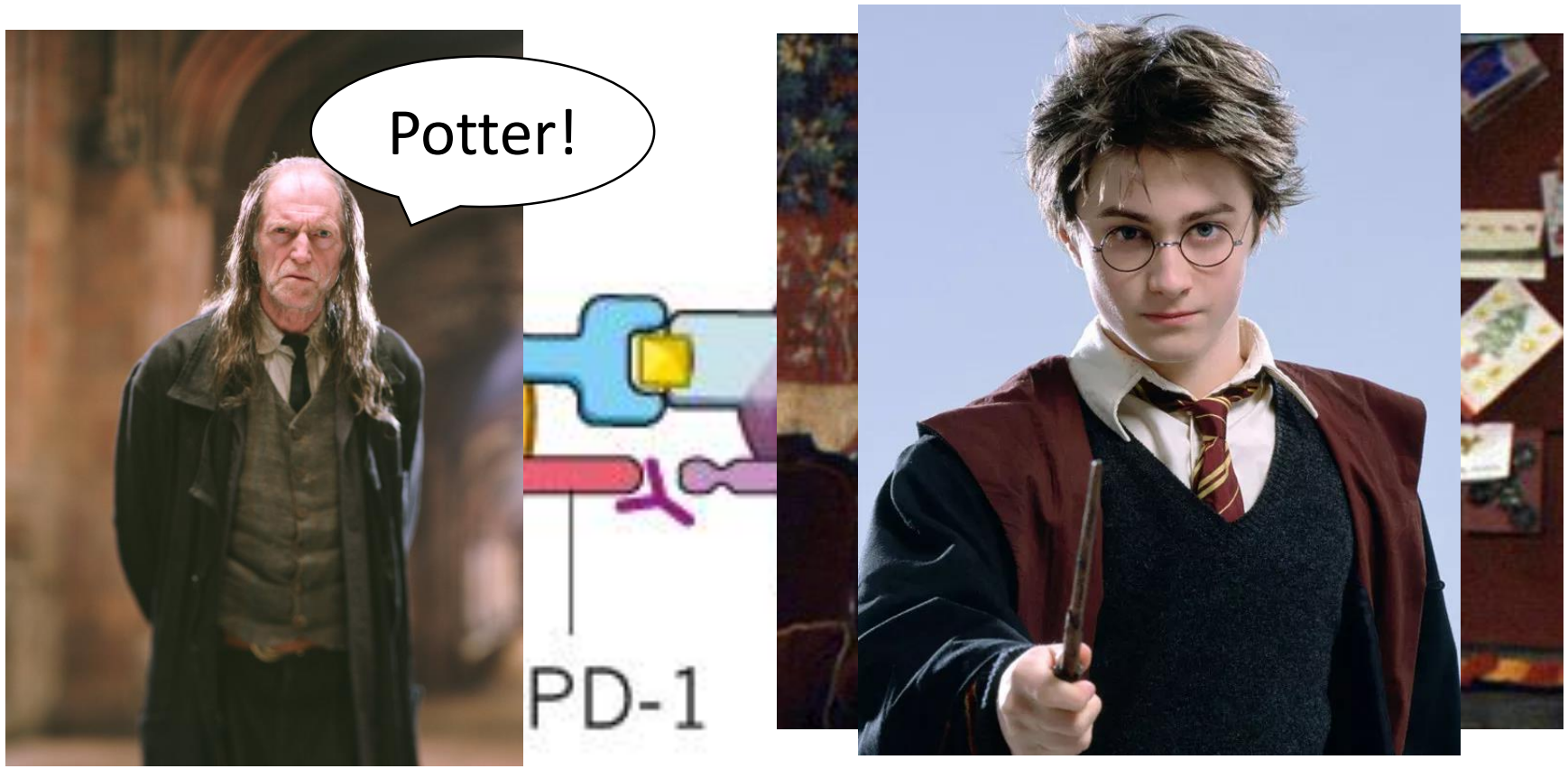


The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

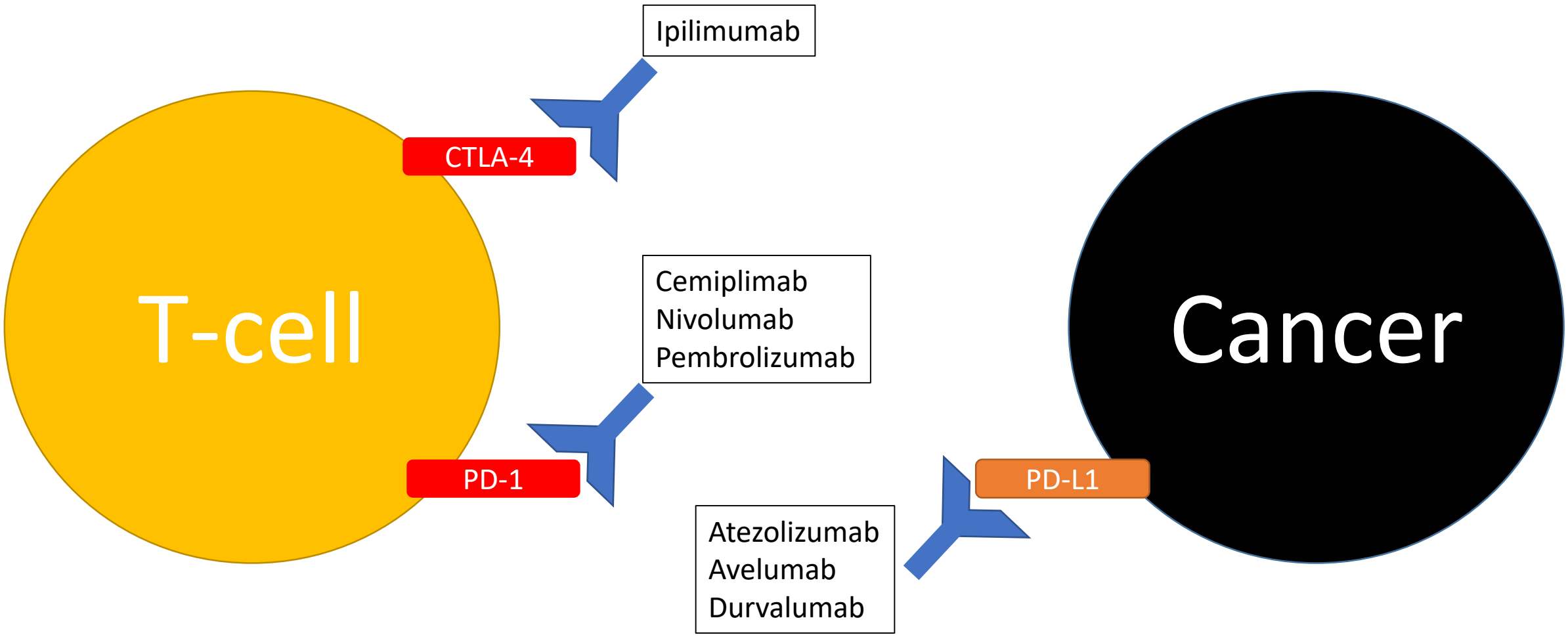


The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.

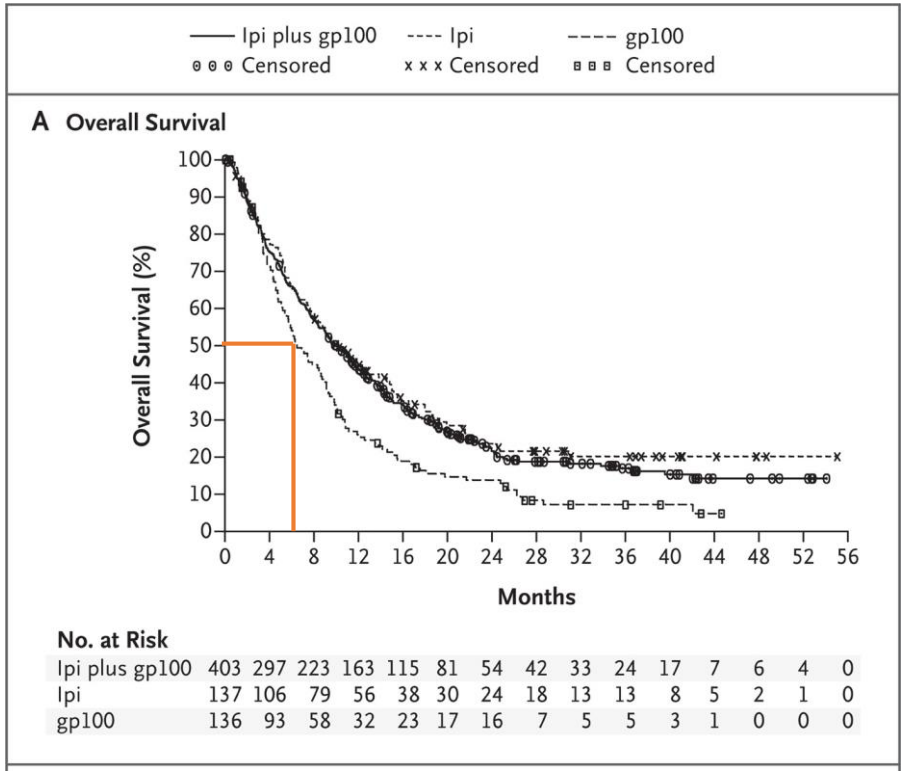
Nature.com

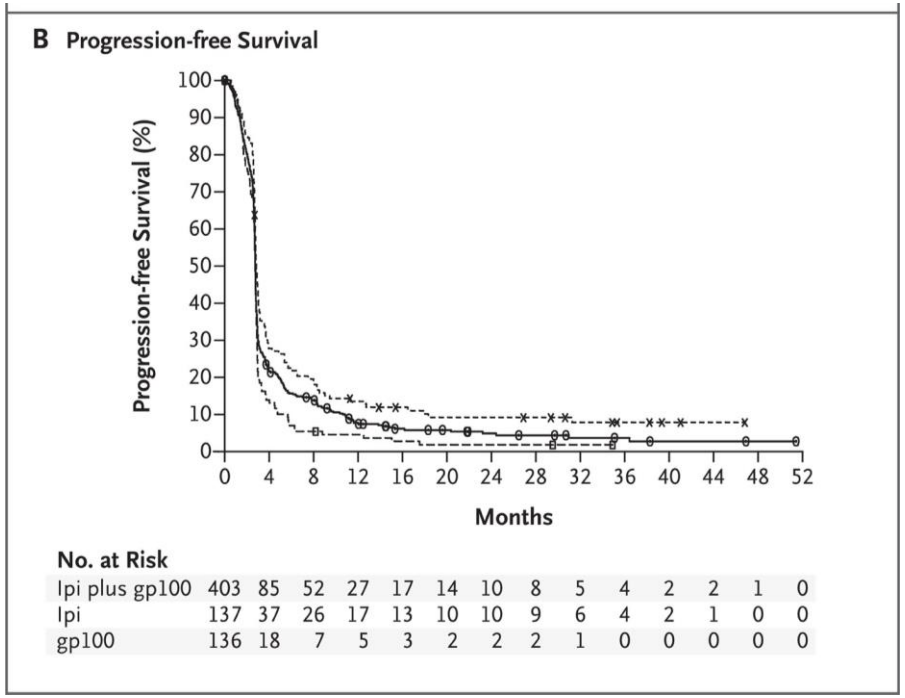


Images from nature.com; Pottermore.com


Ipilimumab
CTLA-4
T-cell
Cemiplimab
Nivolumab
Pembrolizumab
PD-1
Cancer
PD-L1
Atezolizumab
Avelumab
Durvalumab

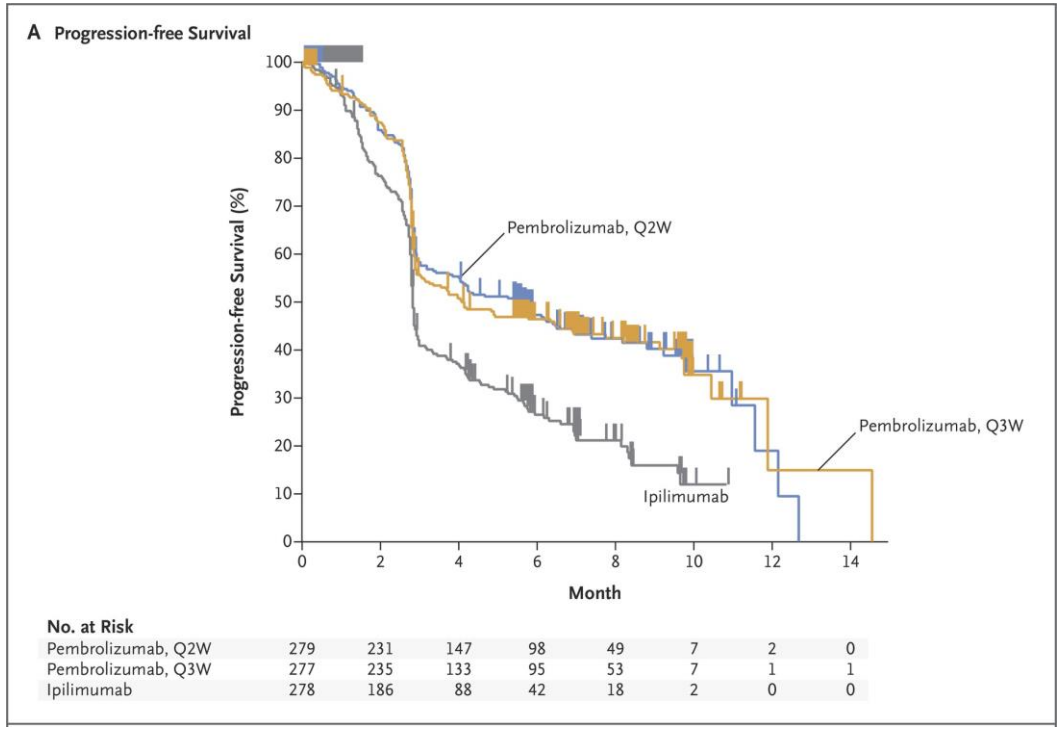
Melanoma: Ipilimumab better than placebo

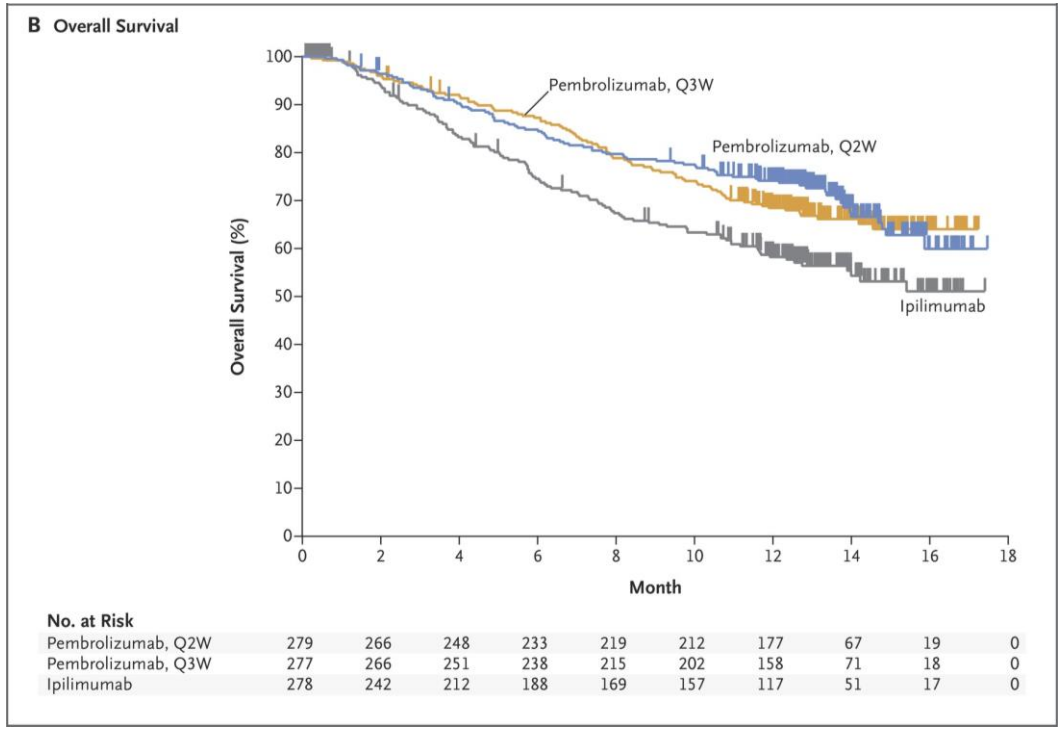




NEJM 2010;363:711-23

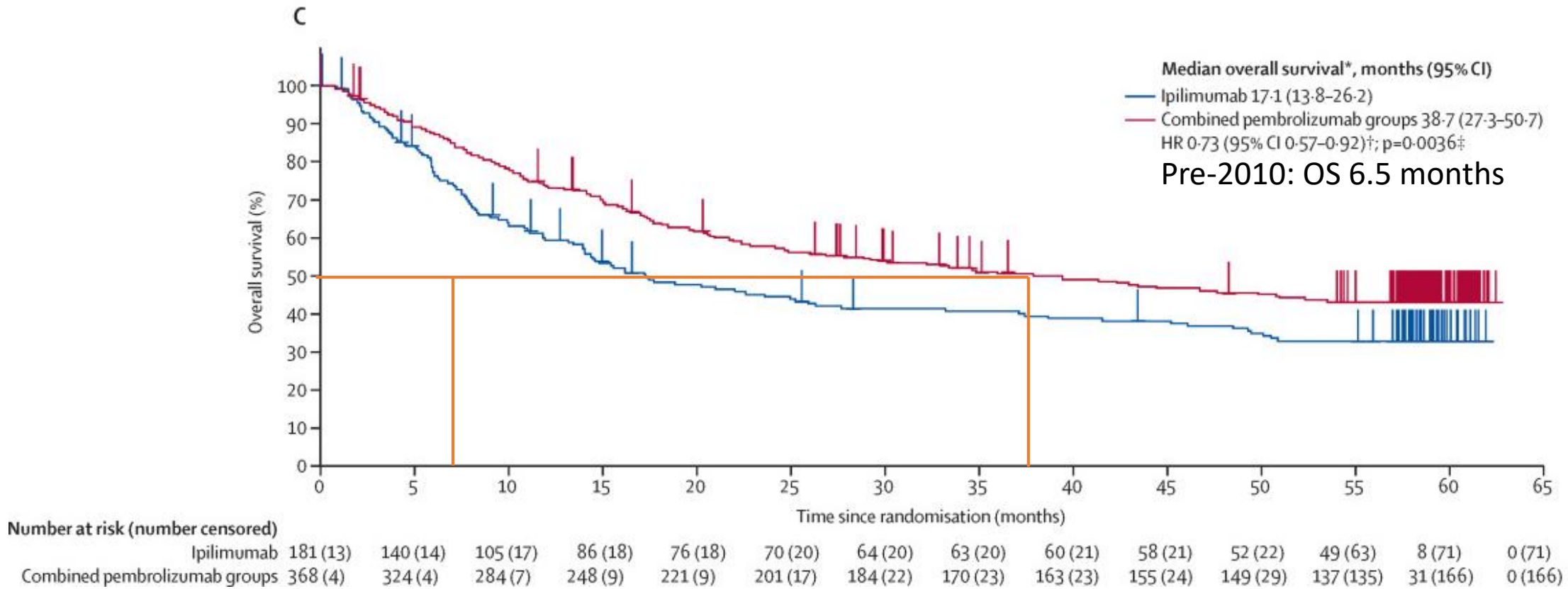
Melanoma: Pembrolizumab better than ipi





NEJM 2015;372:2521-32

Melanoma: responses last!



Pre-2010: OS 6.5 months

Lancet Oncol 2019;20:1239-1251

When do we typically use immunotherapy?

- Melanoma: Adjuvant, relapsed/metastatic
- Non-small cell lung cancer: post-chemoRT, relapsed/metastatic
- Head and neck: relapsed/metastatic
- Renal cell carcinoma: relapsed/metastatic
- Hodgkin’s lymphoma: relapsed
- Hepatocellular: After failure of multikinase inhibitor
- Triple negative breast cancer: relapsed/metastatic


Free
lunch

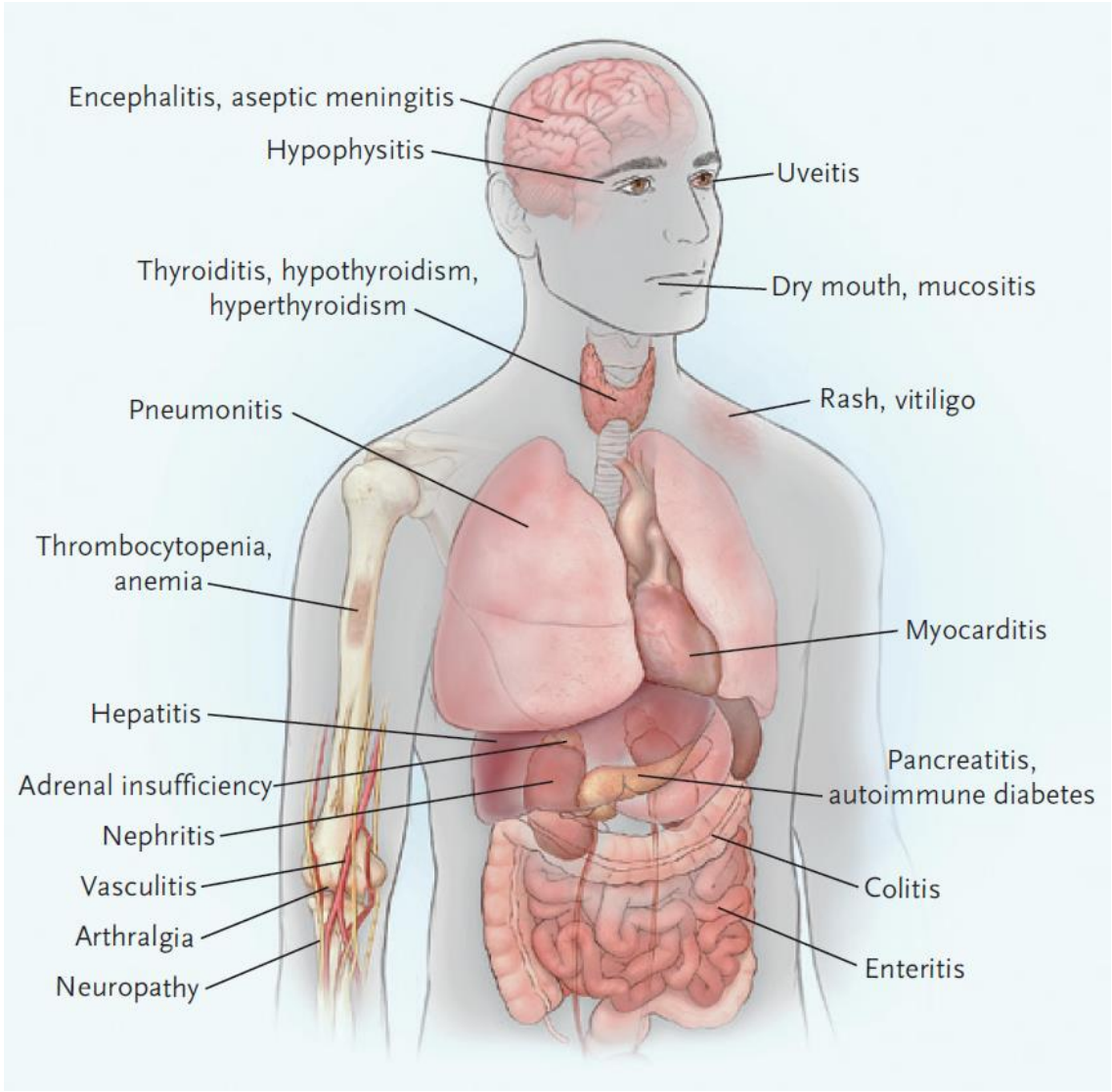
Adverse events (AEs) and Immune related adverse events (irAEs)

Definitions

- Adverse event: side effect associated with a medication
- Immune related adverse event: side effect due to immune activation
- CTCAE: oncology way of grading side effects

Where do irAEs occur?

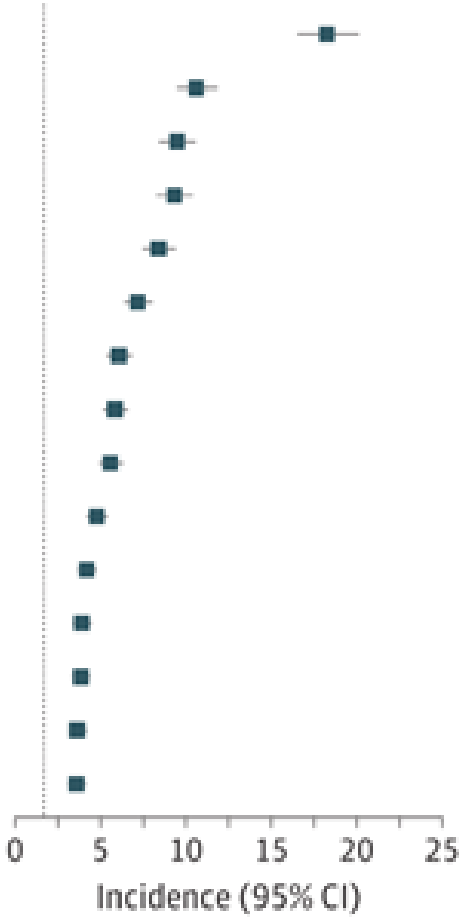
- Any organ system can be affected
- Most commonly gastrointestinal tract, endocrine glands, skin, and liver.
- irAEs require multidisciplinary, collaborative approach for appropriate management



All grade side effects in IO treated patients

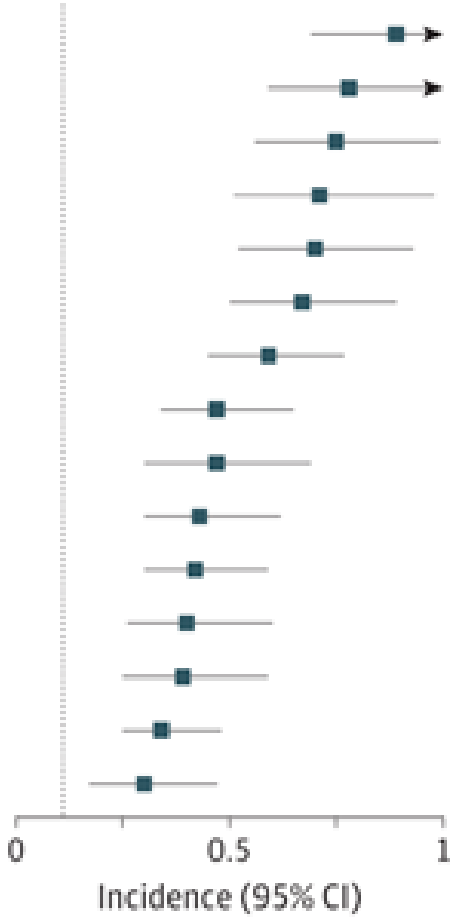
A All-grade adverse event

Event	Incidence (95% CI)
Fatigue	18.26 (16.49-20.11)
Pruritus	10.61 (9.46-11.83)
Diarrhea	9.47 (8.43-10.58)
Rash	9.31 (8.29-10.41)
Nausea	8.39 (7.46-9.39)
Decreased appetite	7.18 (6.36-8.06)
Hypothyroidism	6.07 (5.35-6.85)
Arthralgia	5.83 (5.15-6.59)
Asthenia	5.58 (4.92-6.31)
Pyrexia	4.77 (4.18-5.42)
Cough	4.17 (3.64-4.77)
Dyspnea	3.88 (3.38-4.45)
Anemia	3.84 (3.35-4.38)
Infusion-related reaction	3.63 (3.15-4.17)
Constipation	3.60 (3.12-4.13)



B Grade 3 or higher adverse event

Event	Incidence (95% CI)
Fatigue	0.89 (0.69-1.14)
Anemia	0.78 (0.59-1.02)
AST increased	0.75 (0.56-0.99)
Lipase increased	0.71 (0.51-0.98)
ALT increased	0.70 (0.52-0.93)
Pneumonitis	0.67 (0.50-0.89)
Diarrhea	0.59 (0.45-0.77)
Colitis	0.47 (0.34-0.65)
GGT increased	0.47 (0.30-0.69)
Hepatitis	0.43 (0.30-0.62)
Dyspnea	0.42 (0.30-0.59)
Lymphopenia	0.40 (0.26-0.60)
Hyponatremia	0.39 (0.25-0.59)
Asthenia	0.34 (0.25-0.48)
Amylase increased	0.30 (0.17-0.47)

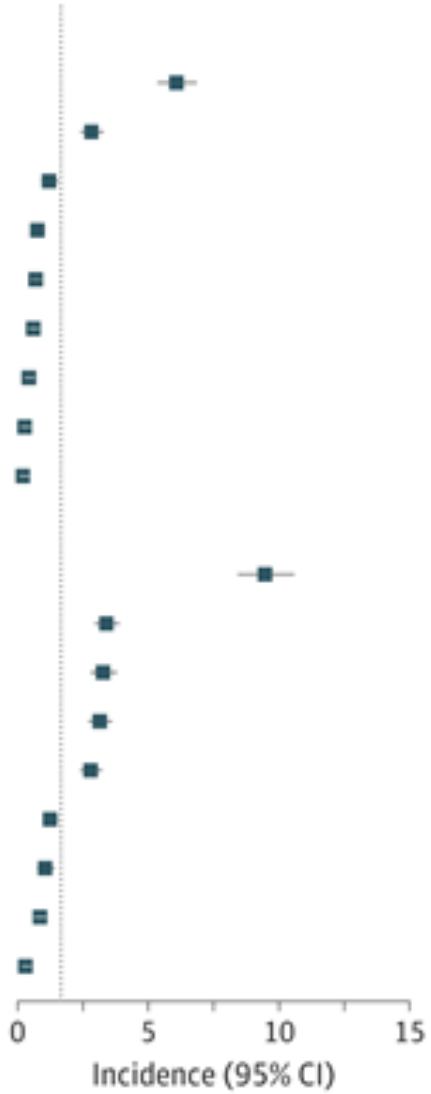


JAMA Oncol 2019;5:1008-1019

Immune related side effect incidence

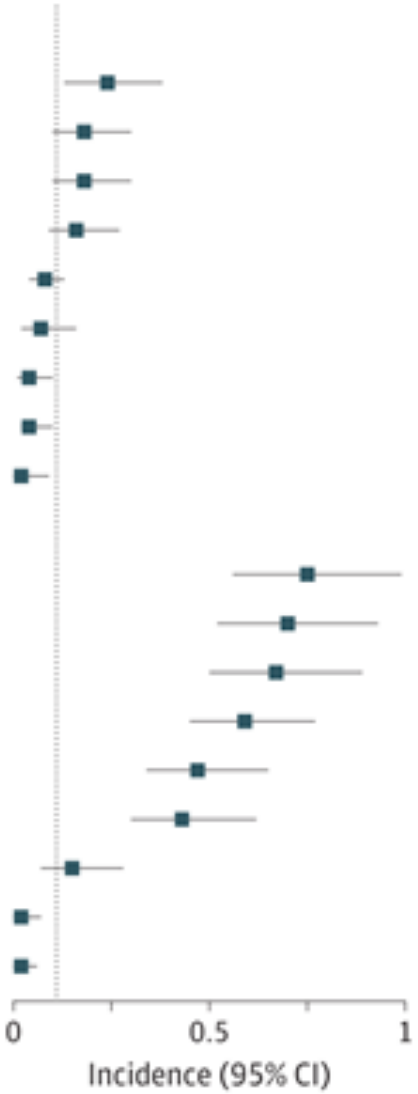
C All-grade irAE

AE	Incidence (95% CI)
Endocrine dysfunction	
Hypothyroidism	6.07 (5.35-6.85)
Hyperthyroidism	2.82 (2.40-3.29)
Hyperglycemia	1.20 (0.91-1.55)
Thyroiditis	0.75 (0.52-1.04)
Adrenal insufficiency	0.69 (0.50-0.93)
Hypophysitis	0.60 (0.42-0.82)
Type 1 diabetes	0.43 (0.27-0.65)
Hypopituitarism	0.26 (0.12-0.50)
Autoimmune thyroiditis	0.20 (0.07-0.45)
Other disorder	
Diarrhea	9.47 (8.43-10.58)
AST increased	3.39 (2.94-3.89)
Vitiligo	3.26 (2.80-3.79)
ALT increased	3.14 (2.71-3.62)
Pneumonitis	2.79 (2.39-3.23)
Colitis	1.24 (0.99-1.54)
Bilirubin increase	1.05 (0.75-1.41)
Hepatitis	0.85 (0.64-1.10)
Uveitis	0.29 (0.15-0.51)



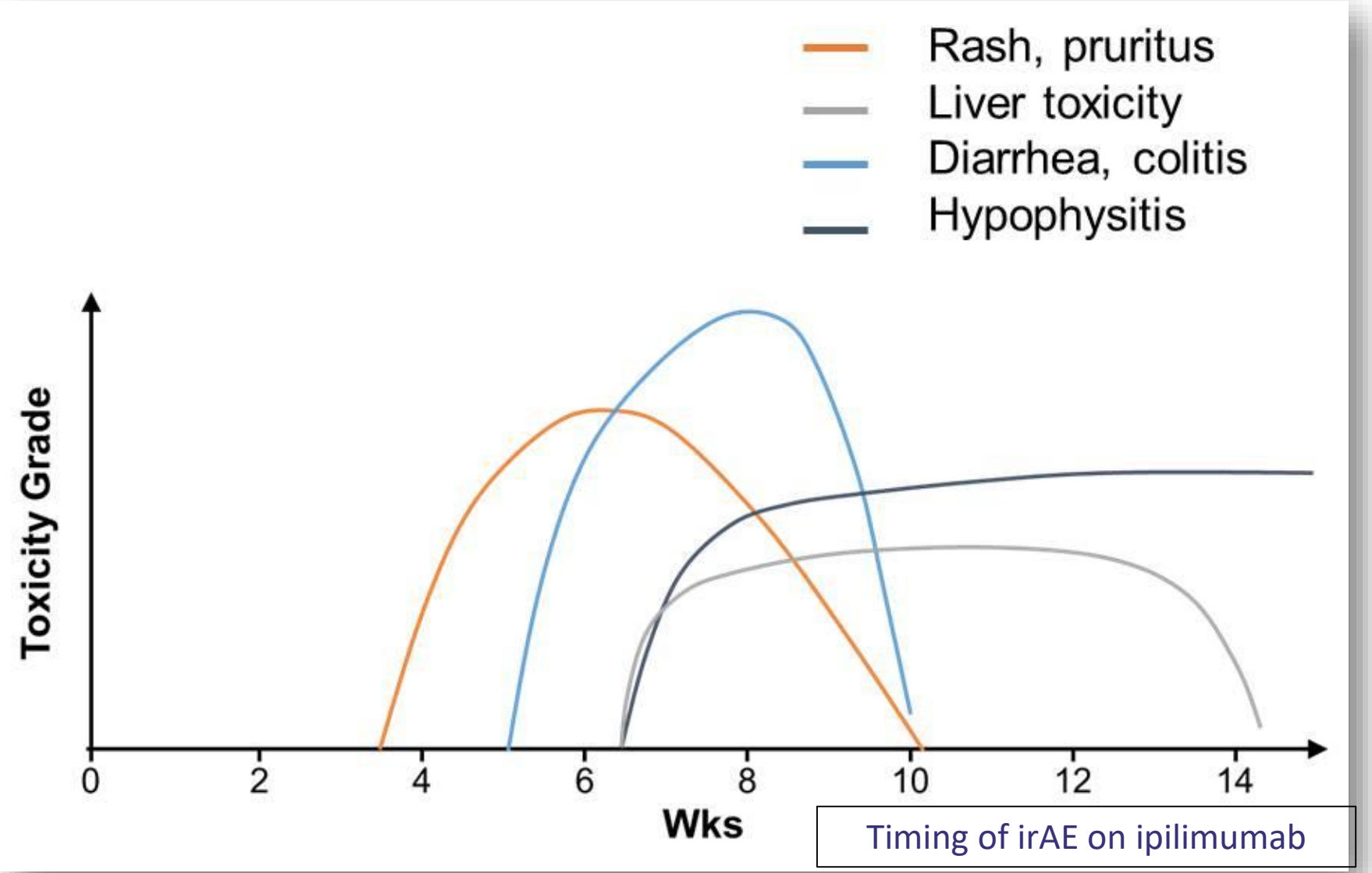
D Grade 3 or higher irAE

AE	Incidence (95% CI)
Endocrine dysfunction	
Hyperglycemia	0.24 (0.13-0.38)
Adrenal insufficiency	0.18 (0.10-0.30)
Type 1 diabetes	0.18 (0.10-0.30)
Hypophysitis	0.16 (0.09-0.27)
Hypothyroidism	0.08 (0.04-0.13)
Hypopituitarism	0.07 (0.02-0.16)
Thyroiditis	0.04 (0.01-0.10)
Hyperthyroidism	0.04 (0.02-0.10)
Autoimmune thyroiditis	0.02 (0.00-0.09)
Other disorder	
AST increased	0.75 (0.56-0.99)
ALT increased	0.70 (0.52-0.93)
Pneumonitis	0.67 (0.50-0.89)
Diarrhea	0.59 (0.45-0.77)
Colitis	0.47 (0.34-0.65)
Hepatitis	0.43 (0.30-0.62)
Bilirubin increase	0.15 (0.07-0.28)
Uveitis	0.02 (0.00-0.07)
Vitiligo	0.02 (0.00-0.06)



JAMA Oncol 2019;5:1008-1019

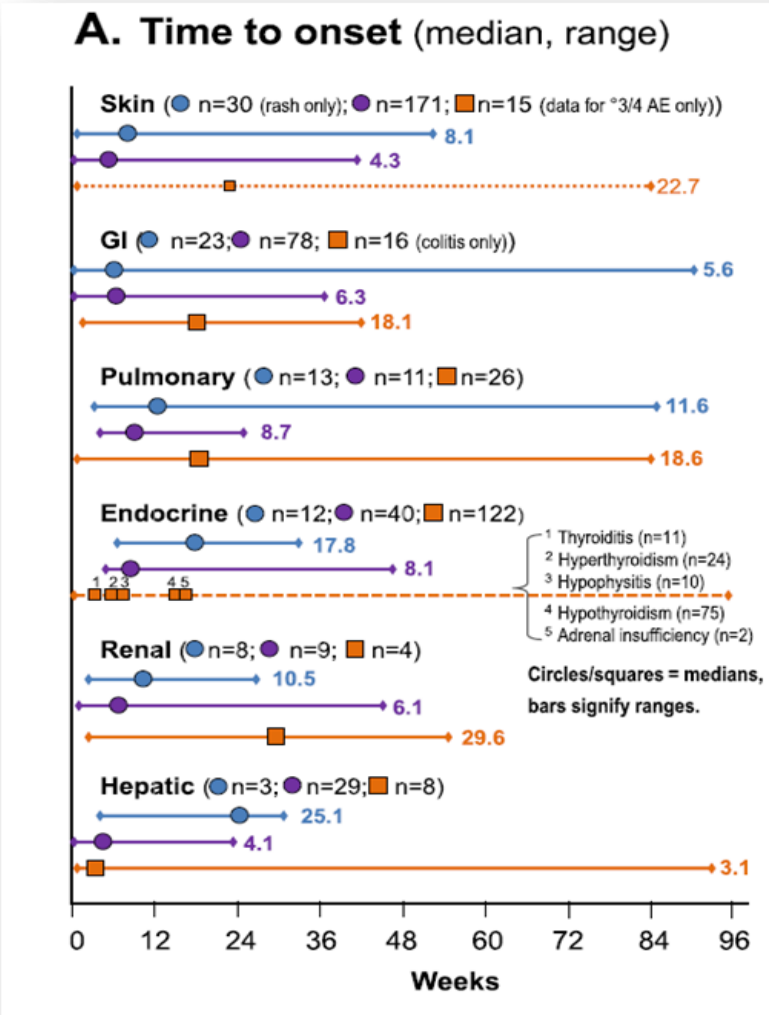
Timing of irAEs

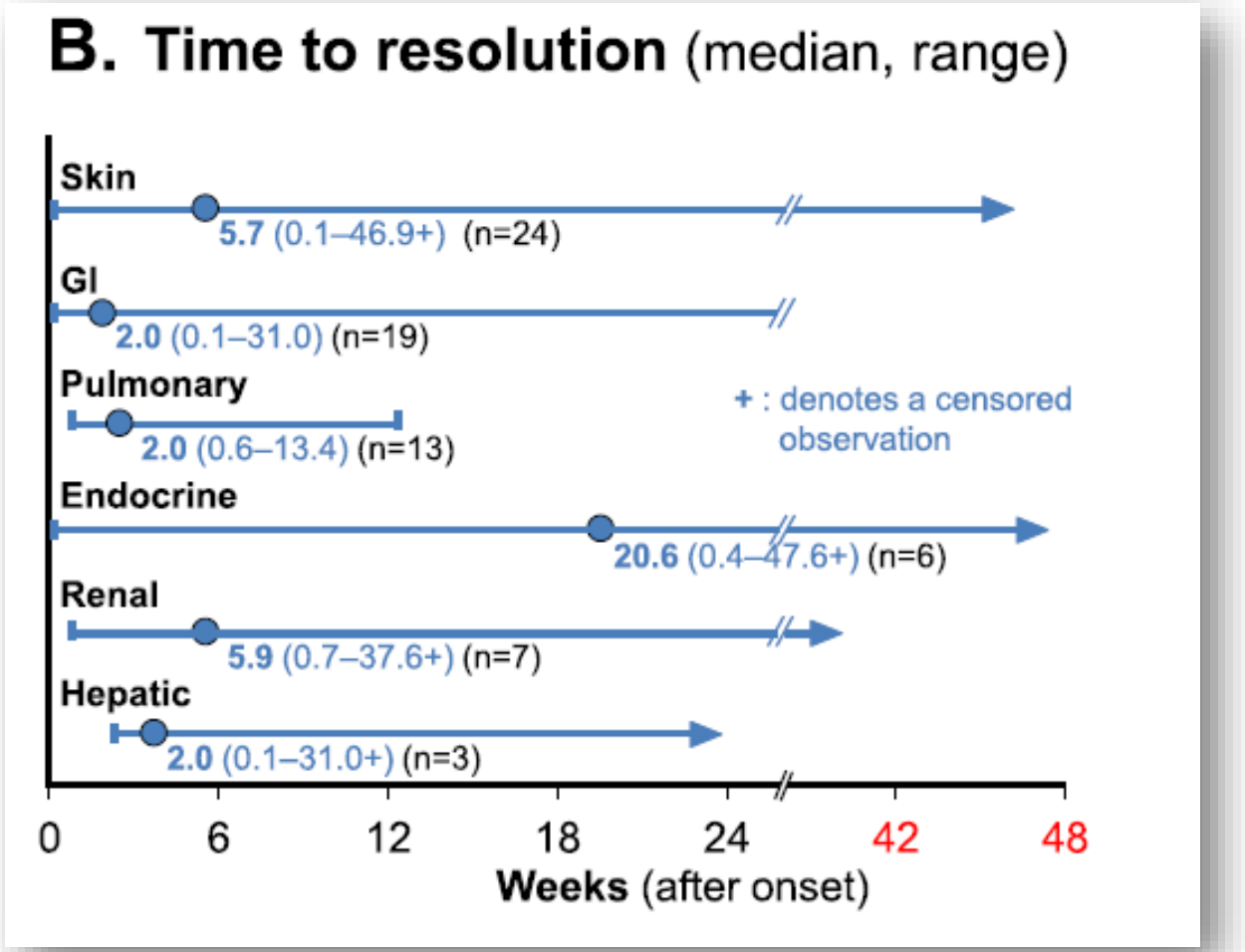


Timing of irAE on ipilimumab

J Clin Oncol 2018; 35:34

Onset and Resolution

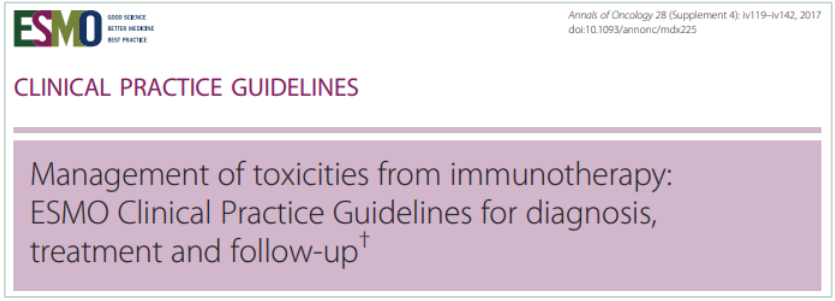




J Clin Oncol 2018; 35:34

Guidelines Galore!

- Multiple guidelines available
  - Choose a set of guidelines and familiarize yourself with them



Guideline websites

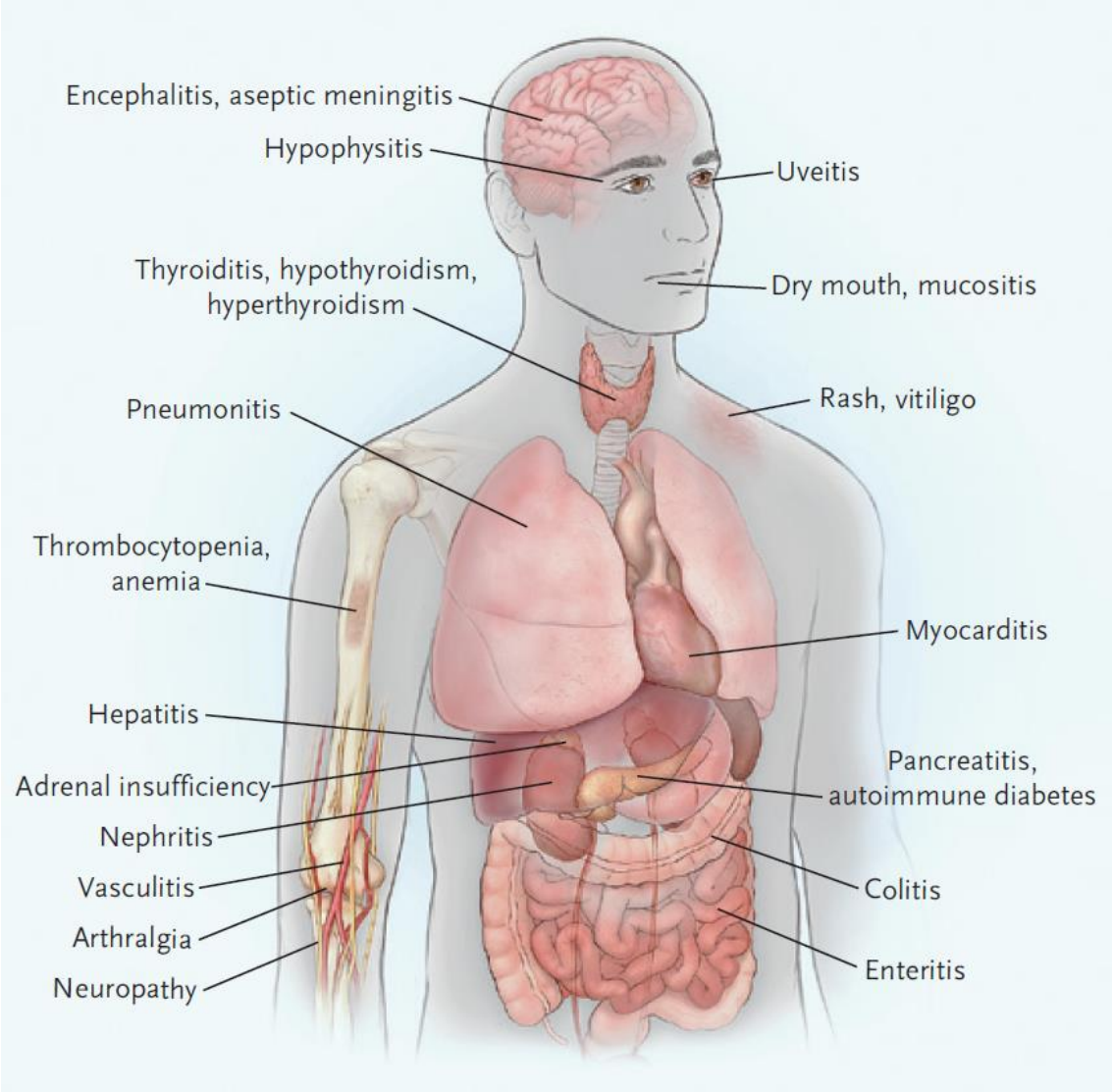
- NCCN: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
- SITC: https://www.sitcancer.org/research/cancer-immunotherapy-guidelines/irae
- ESMO: https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy
- ASCO: https://ascopubs.org/doi/full/10.1200/JCO.2017.77.6385

Management

- Consider stopping/holding the offending medication
- If moderate severity: Prednisone 1-2 mg/kg
- If severe: Methylprednisolone 2 mg/kg/day IV

Big categories of irAEs

- Pulmonary
- Gastrointestinal
- Muco-cutaneous
- Endocrinologic
- MSKL



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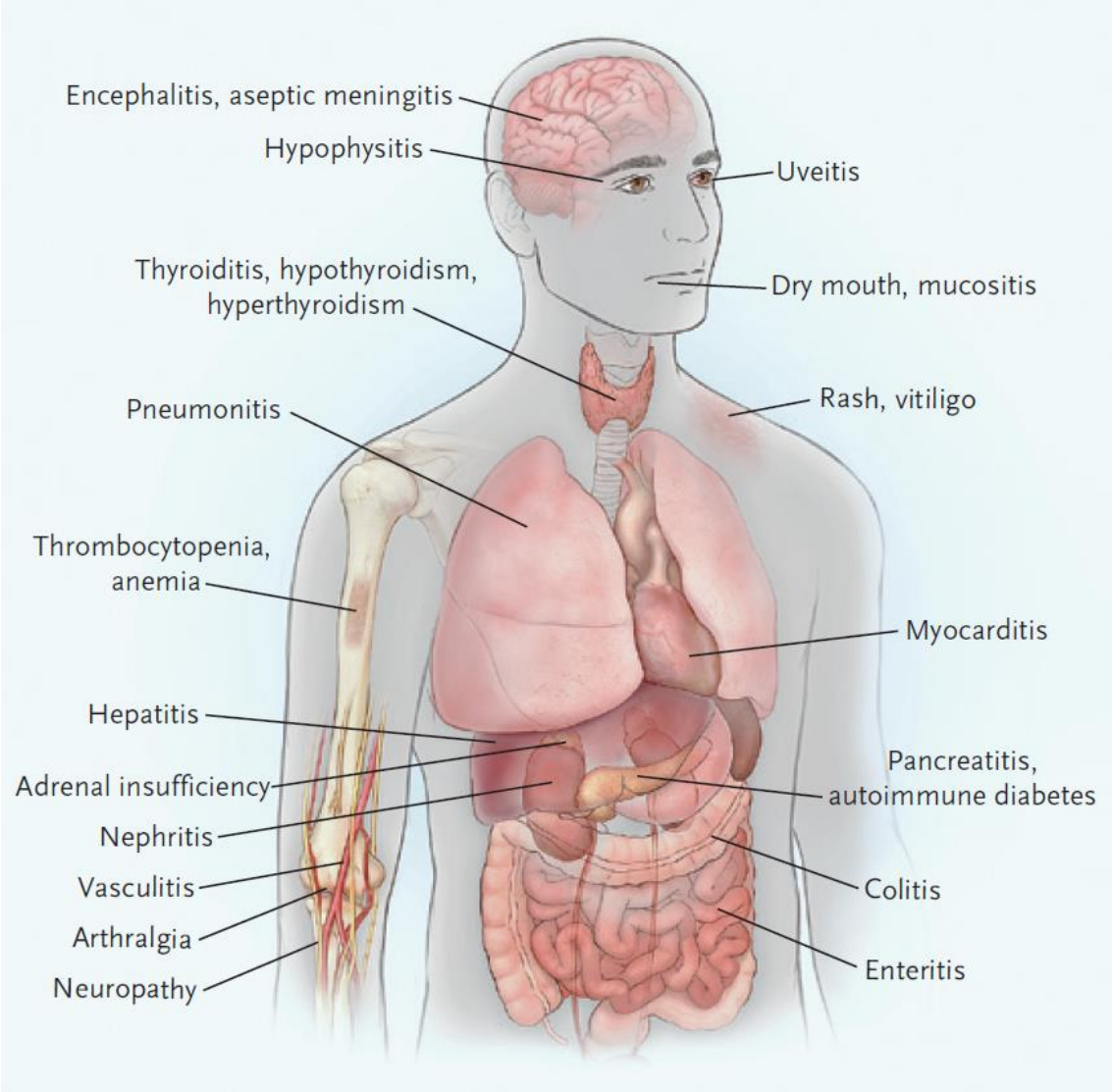

Pneumonitis

- Incidence: 1%–2% of patients treated with PD-1 and/or CTLA-4
- Typical time to onset: 9–19 weeks
- Symptoms: fatigue, cough, dyspnea, hypoxemia (late)
- Differential diagnosis: infection, allergy, cardiac causes (myocarditis)

Eur J Cancer 2016;54:139-48; Cancer Treat Rev 2016;45:7-18.

Pneumonitis

- Workup
  - Chest x-ray and/or CT scan: Radiographic findings of ground-glass lesions and/or disseminated nodular infiltrates
  - Bronchoscopy (if diagnosis in doubt)
  - PFT (pulmonary function testing)
  - Blood gas
- Treatment
  - Steroid therapy (guided by radiographic/symptomatic response)
  - Prophylactic antibiotic/antifungal therapy during high-dose steroid
  - Mycophenolate mofetil, cyclophosphamide, IVIG, or infliximab in severe cases

Eur J Cancer 2016;54:139-48; Cancer Treat Rev 2016;45:7-18.

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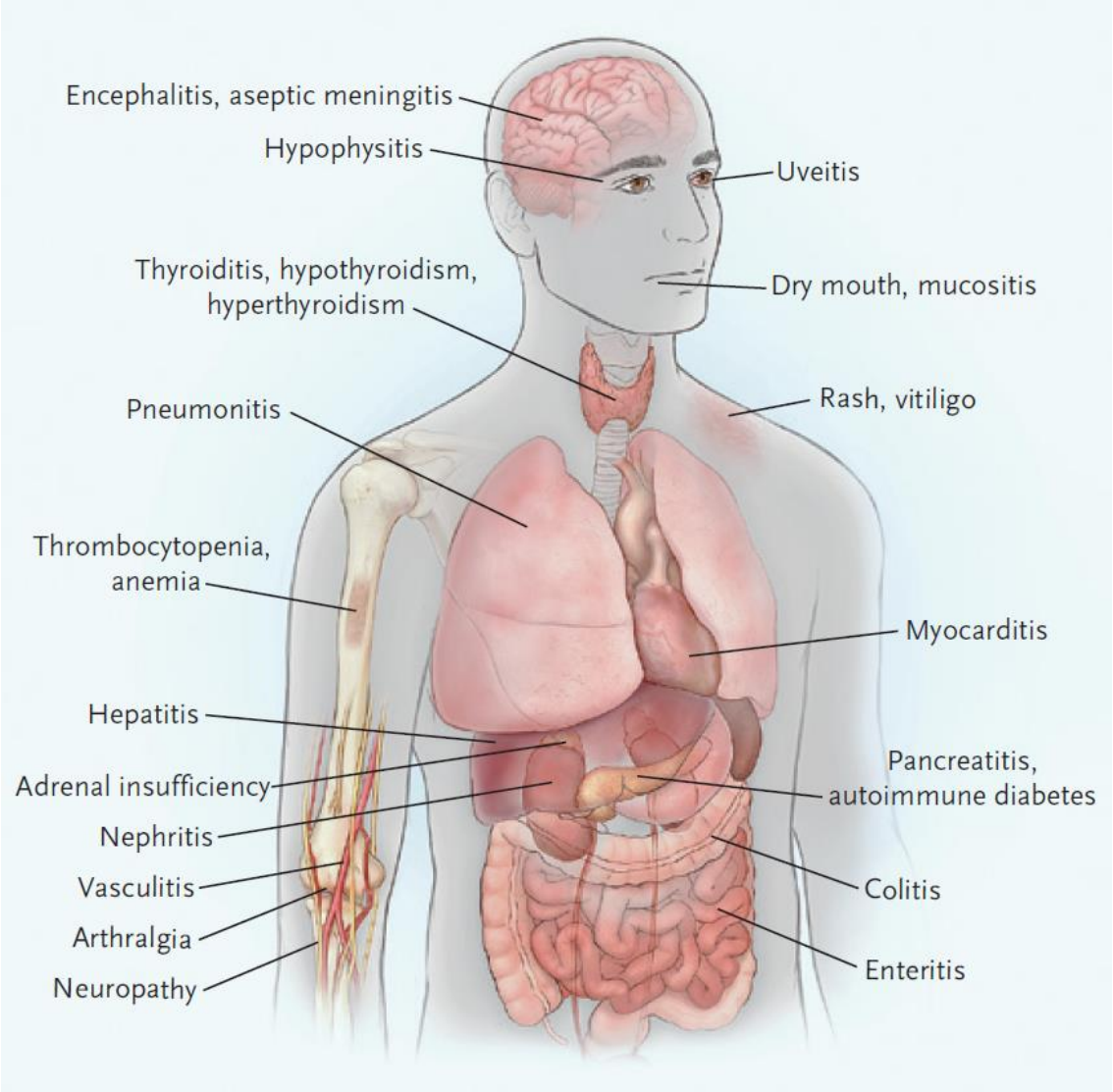


Diarrhea and/or Colitis

- Incidence:
  - Up to 30% with anti-CTLA4 therapy (ipilimumab) with 7% severe
  - Severe in 2% of PD1 pathway drugs (nivolumab, pembrolizumab, etc.)
- Typical time to onset: 6–8 weeks in CTLA-4 or CTLA-4/PD-1, longer in PD-1

NEJM 2010;363:711-23; JAMA Oncology 2016;2:1346-53; NEJM 2015;373:23-34.

Diarrhea and/or Colitis (cont.)

- Symptoms
  - Abdominal cramping, pain
  - Anorexia, dyspepsia
  - Diarrhea +/- blood
  - Possible to have colitis without diarrhea
- Workup
  - Stool for *C. diff*, ova and parasite, blood
  - CT abdomen/pelvis with IV contrast to evaluate for colonic thickening and dilatation
  - Colonoscopy with biopsy if diagnosis unclear

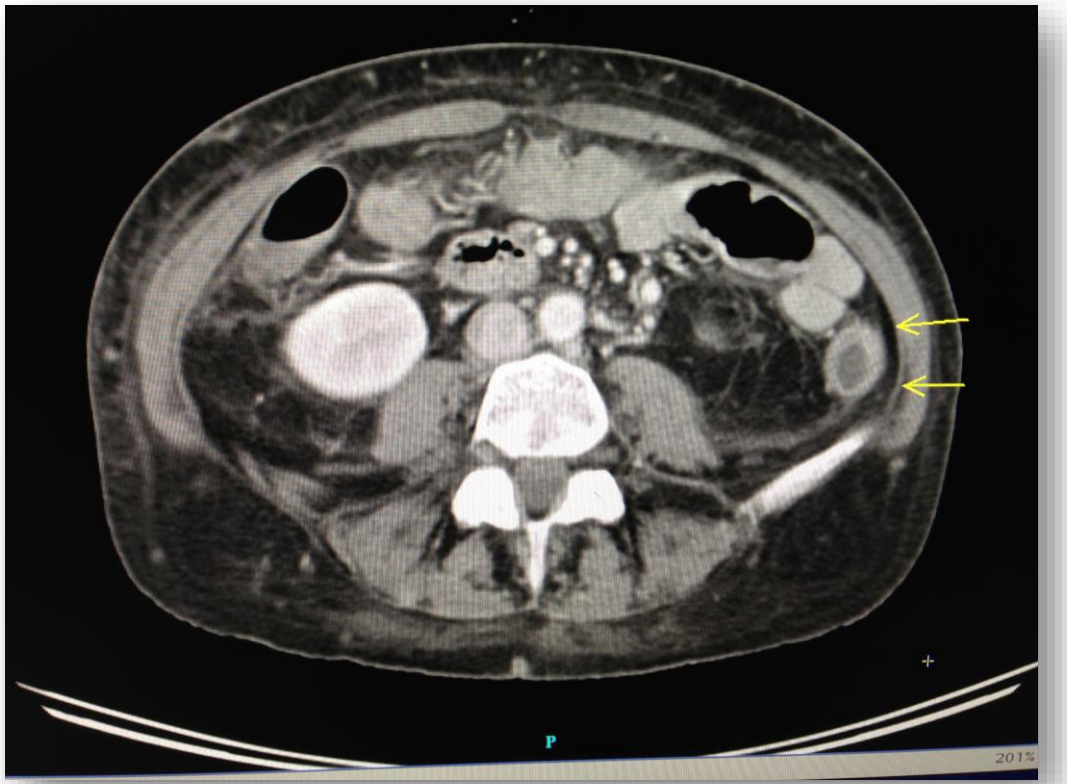
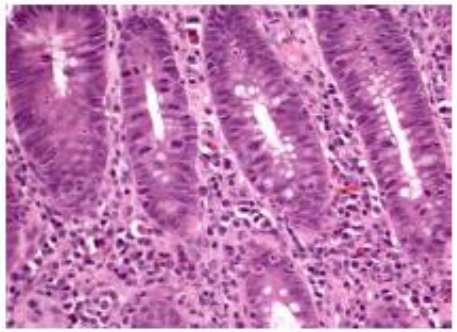


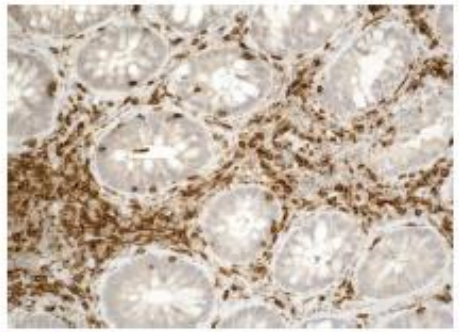
Image courtesy Brianna Hoffner, University of Colorado.

NEJM 2010;363:711-23; JAMA Oncology 2016;2:1346-53; NEJM 2015;373:23-34.

Diarrhea and/or Colitis (cont.)

- Work –up (cont.): Sigmoidoscopy/colonoscopy may be done if diagnosis is unclear





- Treatment:
  - Observation if mild (grade 1)
  - Initial therapy: Steroids (1 mg/kg) if grade 2 or worse (4-6 BMs/day)
  - Diarrhea/colitis with one checkpoint inhibitor does not prohibit use of another

Clin Cancer Res 2009;15:5591-8; JAMA Oncology 2016;2:1346-53.

Hepatitis

- Incidence
  - 2-9% with ipilimumab
  - Approximately 0.5% with anti-PD1
  - Typical time to onset: 8–12 weeks in single agent, sooner in combination
- Symptoms
  - Abdominal bloating or pain, dyspepsia, jaundice, and nausea
  - Usually asymptomatic and diagnosed based on elevated LFT

NEJM 2010;363:711-23; NEJM 2011;364:2517-26; NEJM 2013;368:1365-6; NEJM 2015;373:23-43; JAMA Oncology 2016;2:1346-53.

Hepatitis (cont.)

- Workup
  - Hepatitis panel to evaluate for infectious cause
  - CT and/or ultrasound to evaluate for liver metastases or cholelithiasis
  - Biopsy (if needed)
- Treatment
  - High-dose steroid (prednisone 1–2 mg/kg)
  - Mycophenolate mofetil with steroid for severe cases
  - Infliximab is contraindicated due to hepatotoxic effects[2]
  - Check labs every 1–2 days

NEJM 2010;363:711-23; NEJM 2011;364:2517-26; NEJM 2013;368:1365-6; NEJM 2015;373:23-43; JAMA Oncology 2016;2:1346-53.

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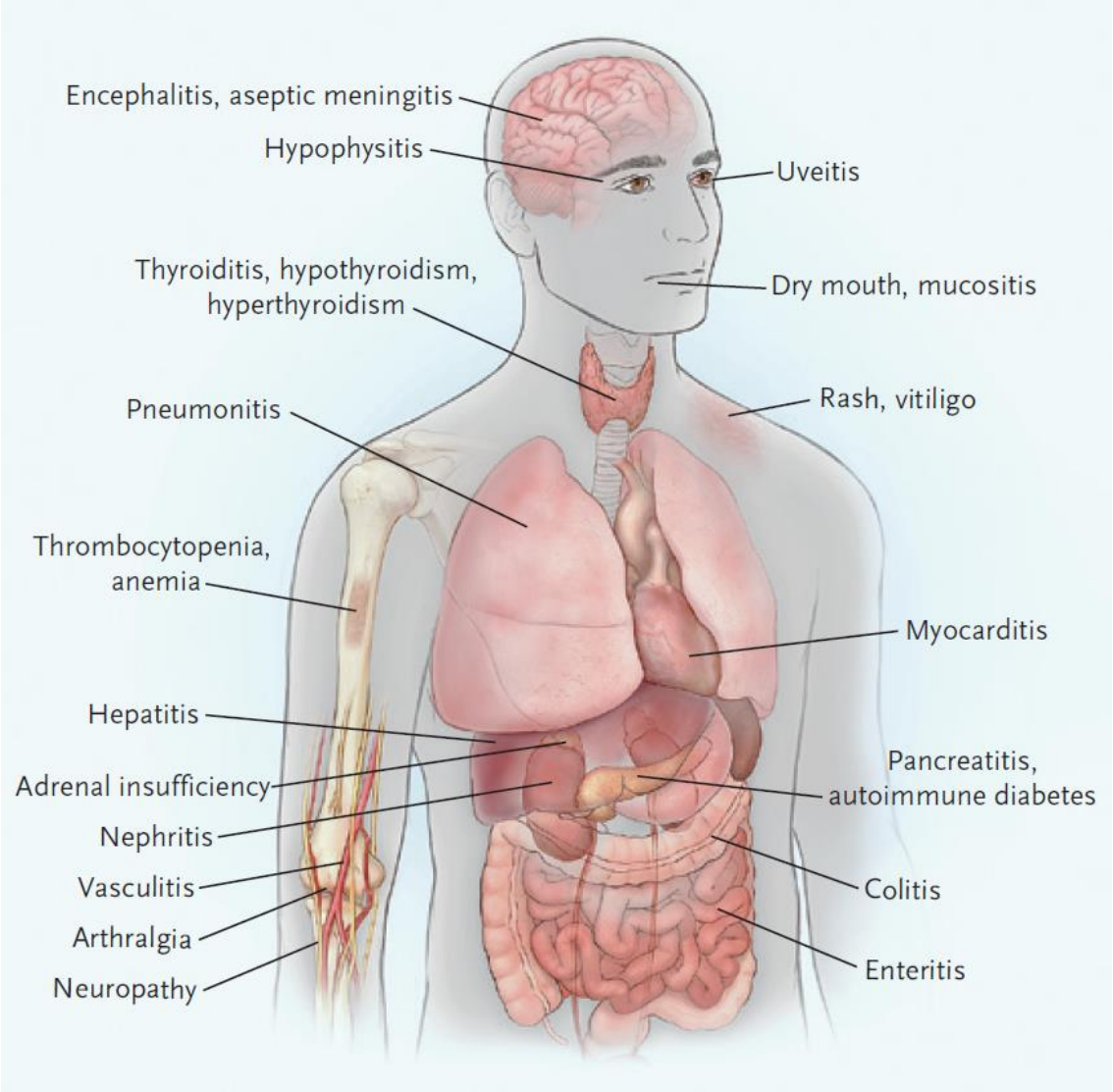

Skin

- Incidence:
  - Most common irAE
  - Anti–PD-1: Approx. 40% in melanoma vs. 17% in NSCLC
- Time to onset: 6 weeks
- Symptoms: Pruritis, vitiligo, rash, erythema
- Work up: biopsy if unclear
- Treatment: topical steroids if mild, systemic if severe

Image courtesy Brianna Hoffner, University of Colorado.

JAMA Oncology 2016;2:1346-53. Cancer Treat Rev 2016;45:7-18

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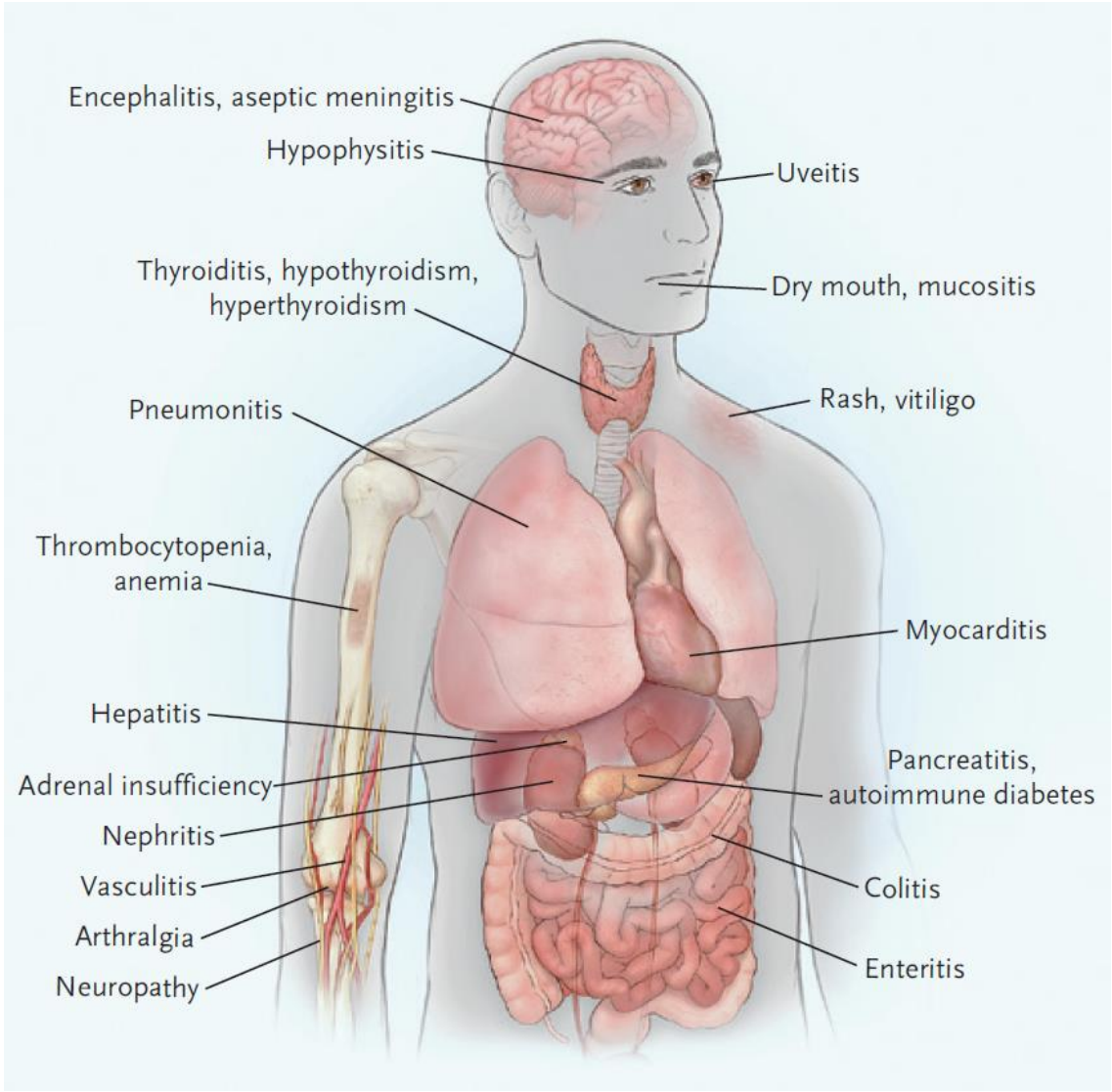


Endocrinopathies

- Incidence: 5%–10% Many endocrine disorders do not resolve, require lifelong replacement
- Median time to onset: Variable (early for thyroid, late for other)
- Symptoms
  - Hypothyroid/hyperthyroid
  - Hypophysitis
  - Adrenal insufficiency
  - Diabetes type 1

Eur J Cancer 2016;54:139-48; Cancer Treat Rev 2016;45:7-18. JAMA Oncol 2019;5:1008-1019. Nat Rev Endocrinol 2017;13:195-207.

Thyroid Disorders

- Incidence: Hypothyroidism in 5-10%
- Typical time to onset: Can be fast (2-4 weeks)
- Symptoms: typical for thyroid disease
- Work up
  - High TSH, low/normal T4 or T3 indicate primary hypothyroidism
  - Low/normal TSH, low T4 suggests hypothyroidism secondary to pituitary
  - TPO antibodies, thyrotropin-binding inhibitory immunoglobulins

TPO = thyroid peroxidase.

Eur J Cancer 2016;54:139-48; Cancer Treat Rev 2016;45:7-18. JAMA Oncol 2019;5:1008-1019. Nat Rev Endocrinol 2017;13:195-207.

Thyroid Disorders (cont.)

- Management
  - Thyrotoxicosis
    - Supportive beta-blockers
    - Hold immunotherapy
    - Radioactive iodine uptake generally inaccurate
    - Generally self-limiting
    - Monitor for subsequent hypothyroidism
  - Hypothyroidism
    - Hormone replacement

Eur J Cancer 2016;54:139-48; Cancer Treat Rev 2016;45:7-18. JAMA Oncol 2019;5:1008-1019. Nat Rev Endocrinol 2017;13:195-207.

Hypophysitis

- Incidence: <5% with PD-1 alone, 10% with combination
- Typical time to onset: >6-12 weeks
- Symptoms: Headache, fatigue, muscle weakness, hypotension, bowel changes
- Work up: Inflammation of the pituitary resulting in low release of all or some of the following pituitary hormones
  - ACTH
  - TSH
  - FSH
  - LH
  - Growth hormone (prolactin)

Eur J Cancer 2016;54:139-48; Cancer Treat Rev 2016;45:7-18. JAMA Oncol 2019;5:1008-1019. Nat Rev Endocrinol 2017;13:195-207.

Hypophysitis (cont.)

- Treatment
  - High-dose steroid for critical illness
  - Low-dose glucocorticoid to alleviate headache/fatigue
  - Replace pituitary hormone deficiencies (start with adrenal insufficiency)
  - Call your friendly, neighborhood endocrinologist

Nat Rev Endocrinol 2017;13:195-207.

Diabetes Mellitus

- Incidence: <5%
- Typical time to onset: 6-12 weeks
- Symptoms: patients generally present in DKA
- Workup
  - CMP, UA
  - GAD65 antibodies
- Treatment: insulin

DKA = diabetic ketoacidosis; GAD65 = glutamic acid decarboxylase 65.

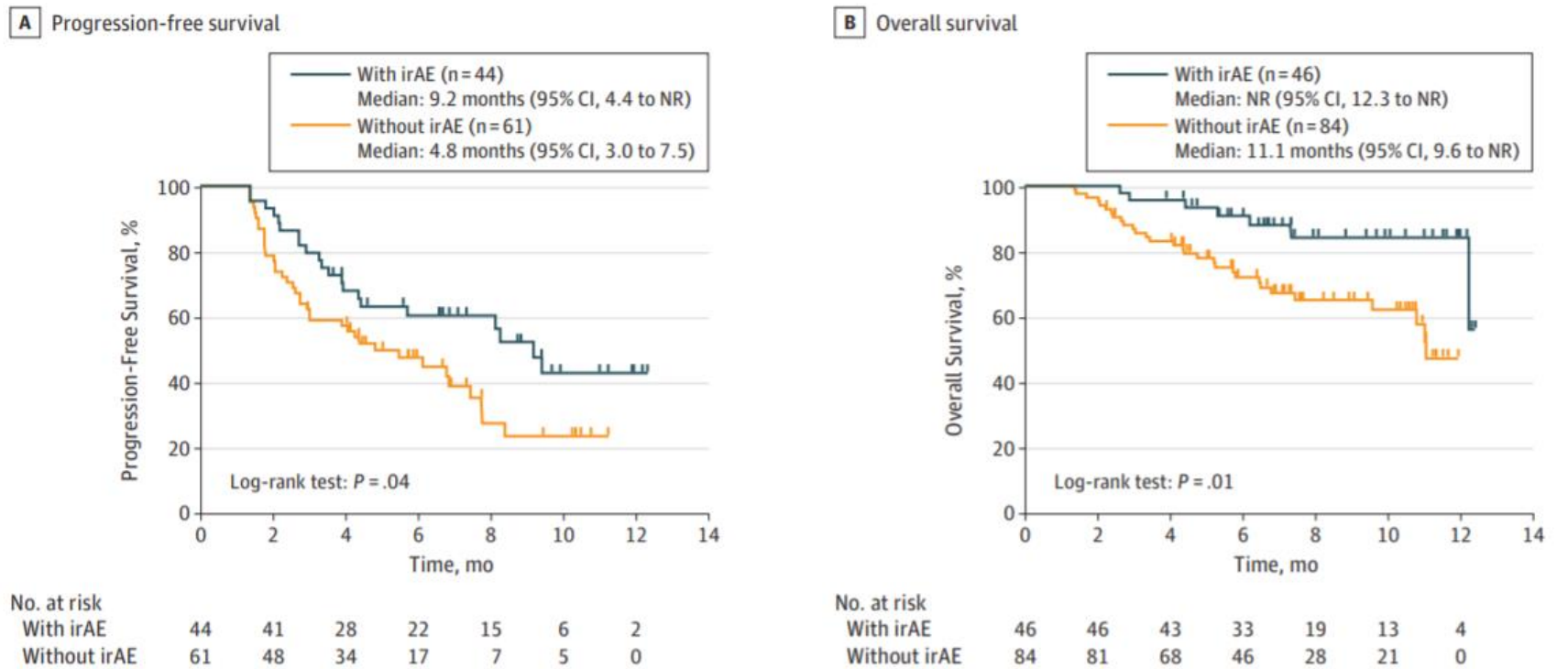
Nat Rev Endocrinol 2017;13:195-207.

irAE summary

- irAE are varied in type, severity and timing
- High index of suspicion for everything
- Steroids are the initial therapy: Prednisone 1-2 mg/kg
- Talk to the oncologist

Fun fact #1: irAE = better response?

Figure. Analysis of Survival for Patients With or Without irAEs



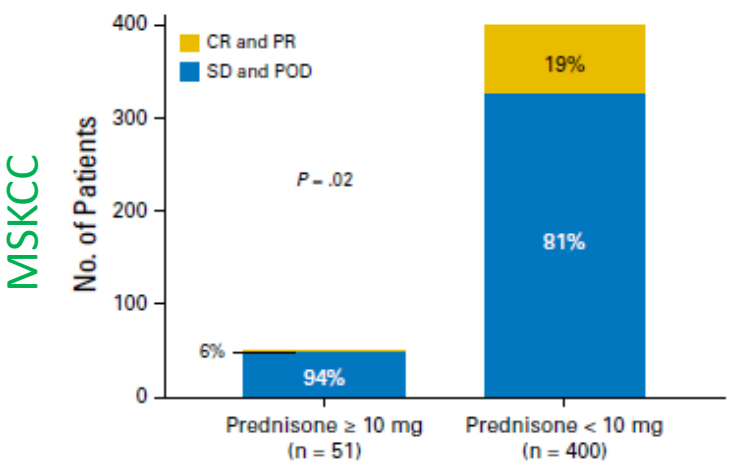
Kaplan-Meier curves with 6-week landmark analysis for (A) progression-free survival (B) and overall survival in patients with or without irAEs. irAEs indicates immune-related adverse events; NR, not reached.

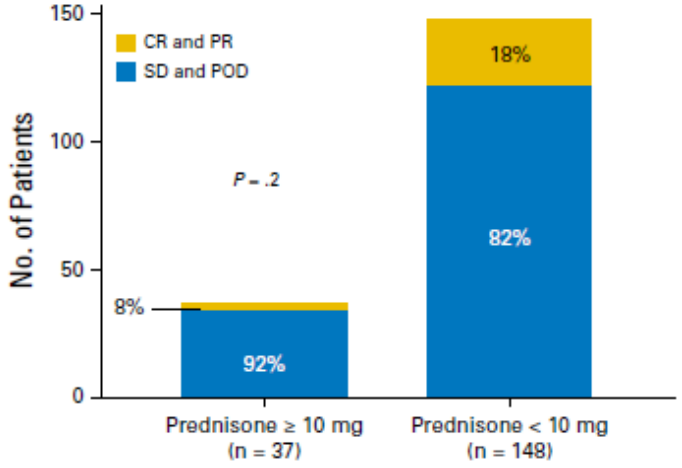
JAMA Oncol 2018;4:374-378.

Fun fact #2: baseline steroids are bad

- Study identified PD-L1 naïve patients with advanced NSCLC from two cancer centers treated with single-agent PD-L1
- Common indications for steroid: dyspnea, fatigue, brain mets
- Baseline corticosteroid /= 10mg prednisone = worse outcome

MSKCC



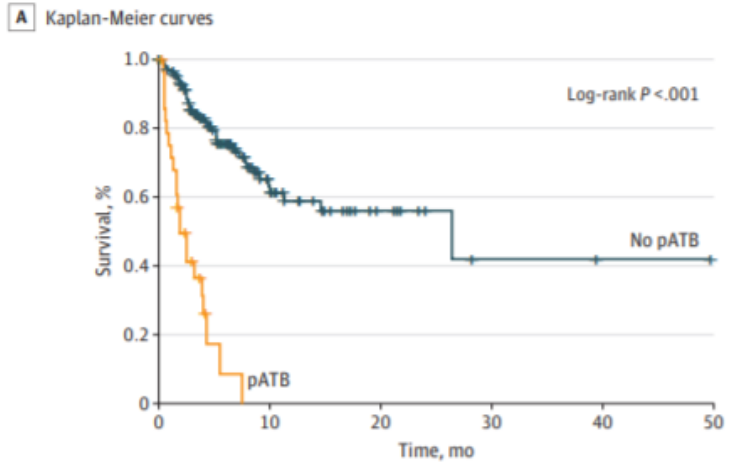


GRCC

J Clin Oncol 2018;36:2872-2878

Fun fact #3: Antibiotics might decrease response

Figure. Association Between pATB Therapy and Survival and Response to ICIs



JAMA Oncol. 2019 Sep 12. doi: 10.1001/jamaoncol.2019.278

Audience response!

Which of the following metastatic cancers is not an indication for immunotherapy?

- ER/PR positive breast cancer
- Head and neck squamous cell carcinoma
- Metastatic melanoma
- Metastatic renal cell carcinoma

Case 1

- 61-year-old man with metastatic non-small cell lung cancer
- Starts single agent pembrolizumab
- After 1 month presents with anxiety, sweating, tremor

Case 1 audience response

Which of the following is the most likely diagnosis?

- Neutropenic fever
- Immune-related thyroid disease
- Immune-related CNS toxicity
- Shaking with excitement to see his oncologist

Case 1 (cont.)

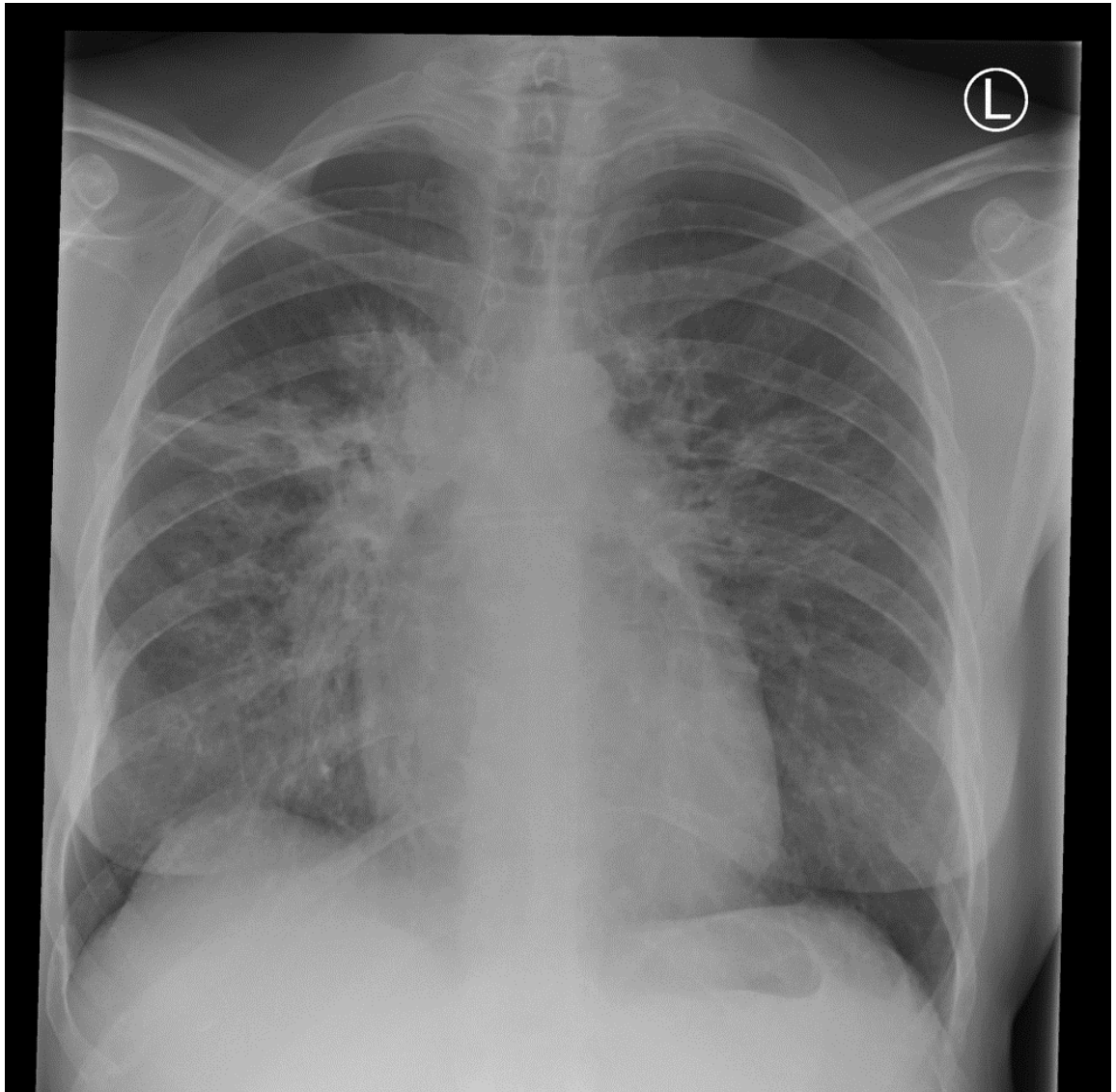
	Pre-tx	1 month	2 months	3 months
TSH	1.9	<0.076	<0.0005	8.14 (H)
Free T4	0.82 (L)	1.42	3.19 (H)	0.46 (L)

Hold immunotherapy
Start metoprolol

Case 2

- 56 y/o man with metastatic renal cell
- Starts single agent nivolumab
- At 10 weeks presents to PCP with cough, SOB, hypoxemia

Case 2 (cont.)



Case 2 audience response

- Which of the following is not appropriate?

- Stop nivolumab
- Start prednisone 2 mg/kg
- Call your patient’s oncologist
- Start infliximab

Case 2 (cont.)

- Workup
  - Call your friendly oncologist
  - CT scans
- Management
  - Prednisone 1-2 mg/kg
  - Consider antibiotics

Case 3

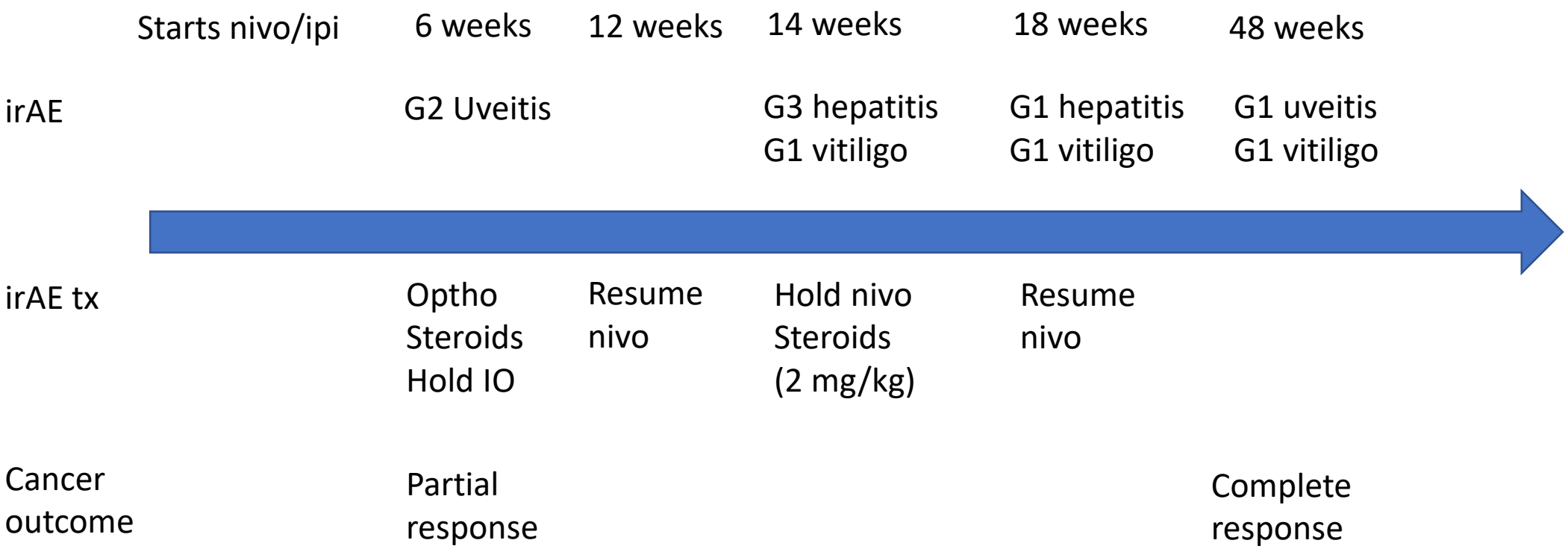
- 49 y/o man with metastatic melanoma
- Starts nivolumab + ipilimumab
- After 2 month
  - Massive neck tumors almost gone
  - Complains of progressive vision loss

Case 3 audience response

What should you do next?

- Non-urgent ophtho referral for cataracts
- Urgent ophtho referral for evaluation
- Modify his anti-hypertensive regimen

Case 3 (cont.)


Starts nivo/ipi
6 weeks
12 weeks
14 weeks
18 weeks
48 weeks
irAE
G2 Uveitis
G3 hepatitis
G1 vitiligo
G1 hepatitis
G1 vitiligo
G1 uveitis
G1 vitiligo
irAE tx
Optho
Steroids
Hold IO
Resume
nivo
Hold nivo
Steroids
(2 mg/kg)
Resume
nivo
Cancer
outcome
Partial
response
Complete
response

Learning summary

- Describe some basic biology of how immunotherapy works
- Identify the benefits of immunotherapy in cancer
- Recognize immunotherapy side effects and how to treat them