JADPRO CE Regional Lectures

Clinical Advances and Case Studies in Immune Checkpoint Inhibitors in Oncology

Immune-Related Adverse Events

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Faculty Financial Disclosures

- Ms. Hoffner has received consulting fees/honoraria from Abbott, Array BioPharma, and Merck.
- Ms. Zitella has served on the advisory board for Array Biopharma and has equity interests/stock options in Kite Pharma.
- Dr. Lewis has nothing to disclose.

Planning Committee Financial Disclosures

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Learning Objectives

- Differentiate between early and late adverse effects associated with immunotherapeutic agents.

Audience Response Question

Which of the following is true regarding immune-related adverse events?

A) Endocrine-related adverse events are usually the first to appear
B) Dermatologic-related adverse events are associated with a better response in patients with lung cancer
C) Patients with melanoma are more likely to develop pneumonitis than patients with other cancers
D) The incidence of specific adverse events varies based on the underlying cancer
E) Unsure

Audience Response Question

Your patient with melanoma receiving treatment with anti–PD-1 therapy develops a grade 2 dermatitis not responsive to topical therapy. You educate the patient that:

A) We will need to hold immunotherapy and treat the dermatitis with oral steroid. Oral steroid may decrease the efficacy of anti–PD-1 therapy.

B) We will need to hold immunotherapy and treat the dermatitis with oral steroid, but that the efficacy of immunotherapy is unaffected.

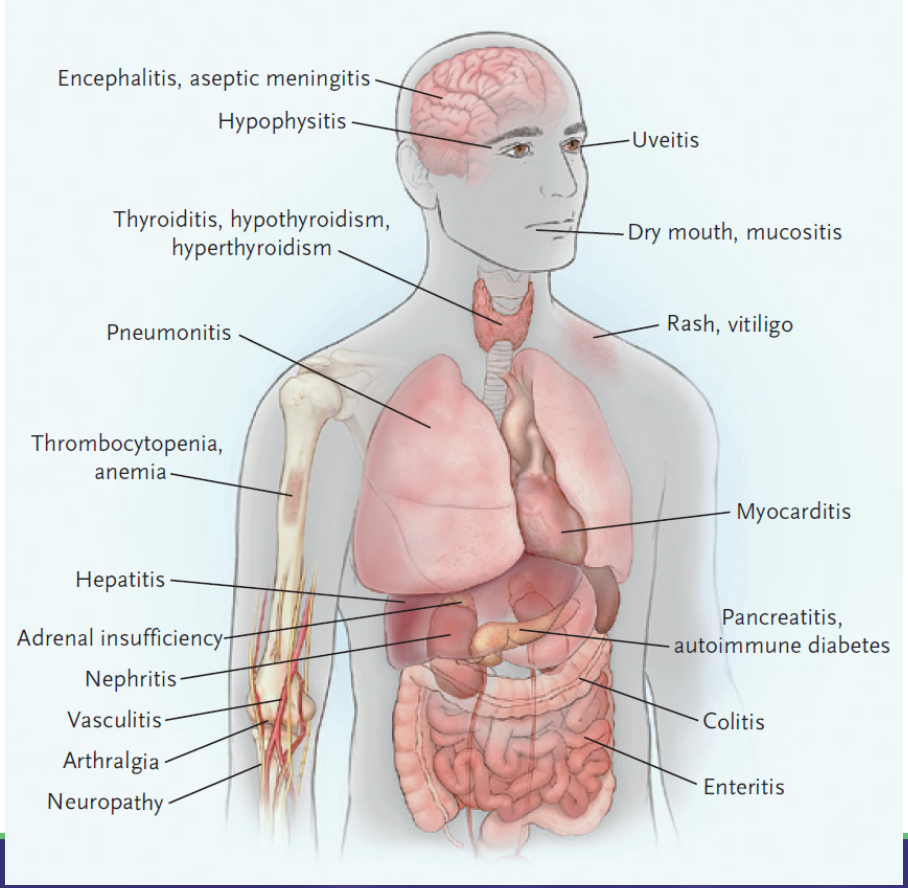
C) We will continue immunotherapy and treat the dermatitis with oral steroid. Oral steroid may decrease the efficacy of anti–PD-1 therapy

D) We will continue immunotherapy and treat the dermatitis with oral steroid, but that the efficacy of immunotherapy is unaffected

E) Unsure

Where do irAEs occur?

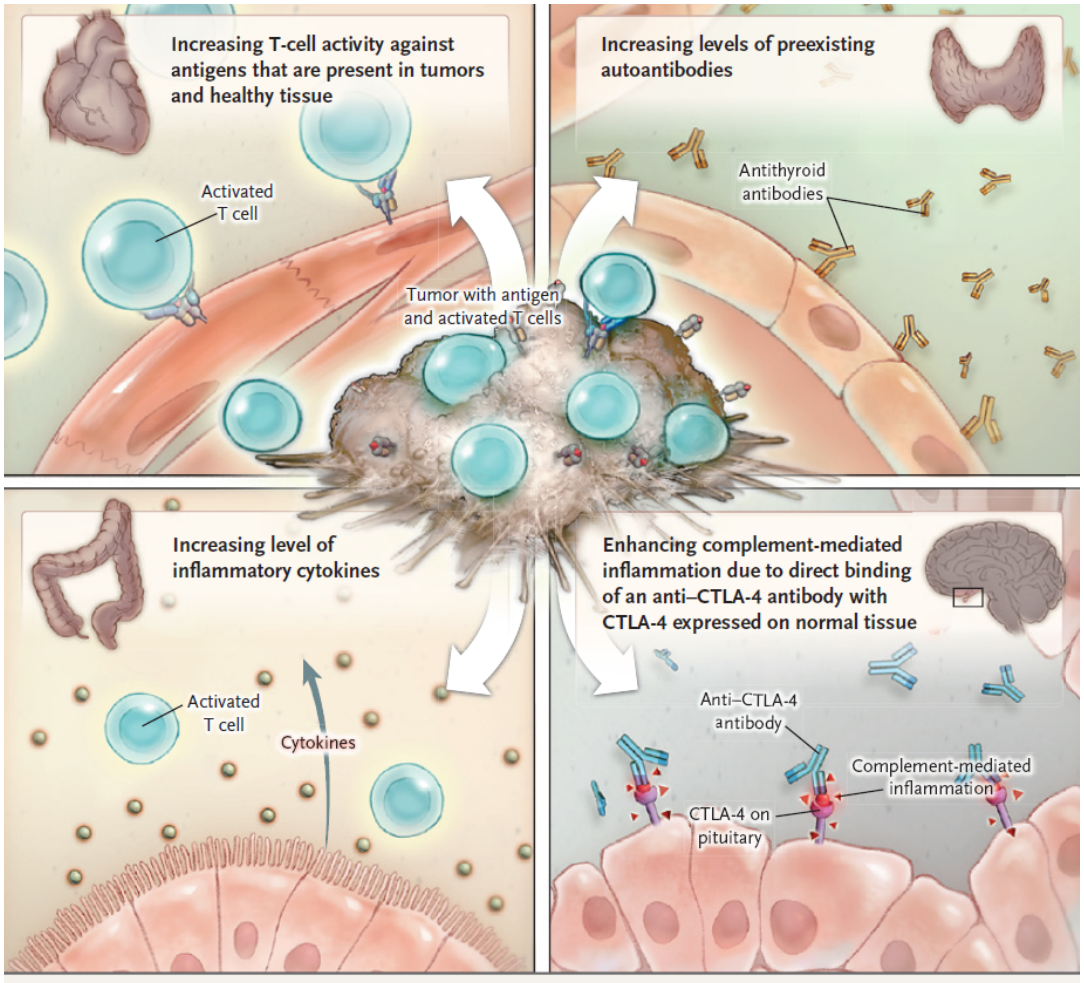
- Any organ system can be affected
- Most commonly gastrointestinal tract, endocrine glands, skin, and liver.
- irAEs require multidisciplinary, collaborative approach for appropriate management



Postow et al. (2018). Immune-related adverse events associated with immune checkpoint blockade. *NEJM*, 378(2).

Mechanisms Underlying irAEs

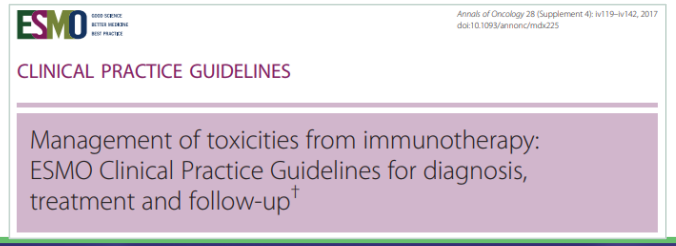
- Likely multiple mechanisms
- Differences among classes
  - More colitis and hypophysitis with CTLA-4
  - More pneumonitis and thyroiditis with PD-1
- Differences among histologies
  - More vitiligo in melanoma



Postow et al. (2018). Immune-related adverse events associated with immune checkpoint blockade. *NEJM*, 378(2).

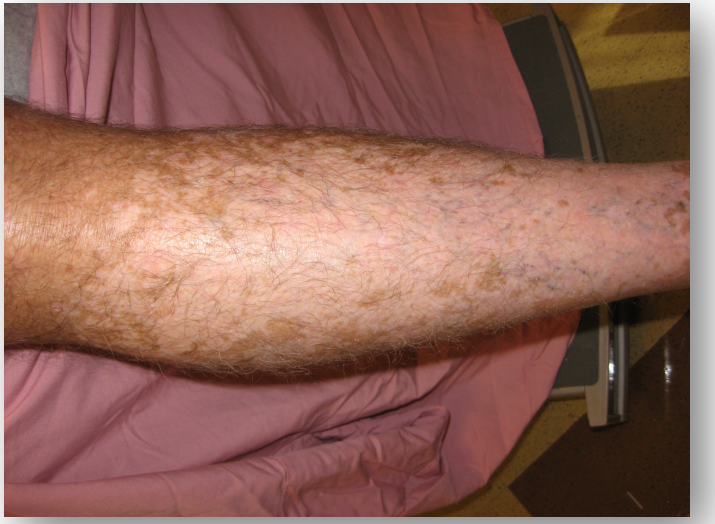
Guidelines Galore!

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



Skin

- Skin events most frequent irAE for both anti–CTLA-4 and anti–PD-1 blockade in melanoma patients
  - Anti–PD-1: Approx. 40% in melanoma vs. 17% in NSCLC[1]
- More common in anti–CTLA-4 (50%) and combo (60%)[2]
  - Grade 3/4 rash in less than 10%[2]
- Includes vitiligo, rash, erythema
  - Rarely Stevens-Johnson syndrome or toxic epidermal necrosis



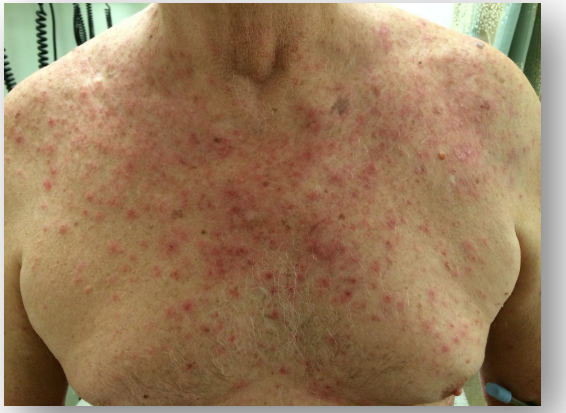
irAE = immune-related adverse event

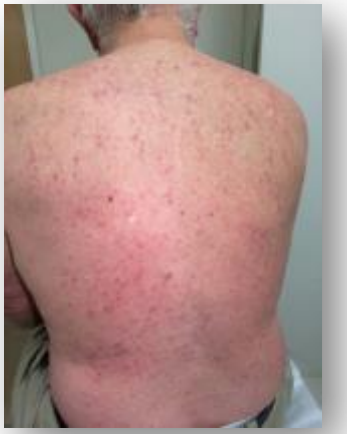
1. Eigentler TK, et al. *Cancer Treat Rev* 2016;45:7-18; 2. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53.

Image courtesy Brianna Hoffner, University of Colorado.

Dermatitis

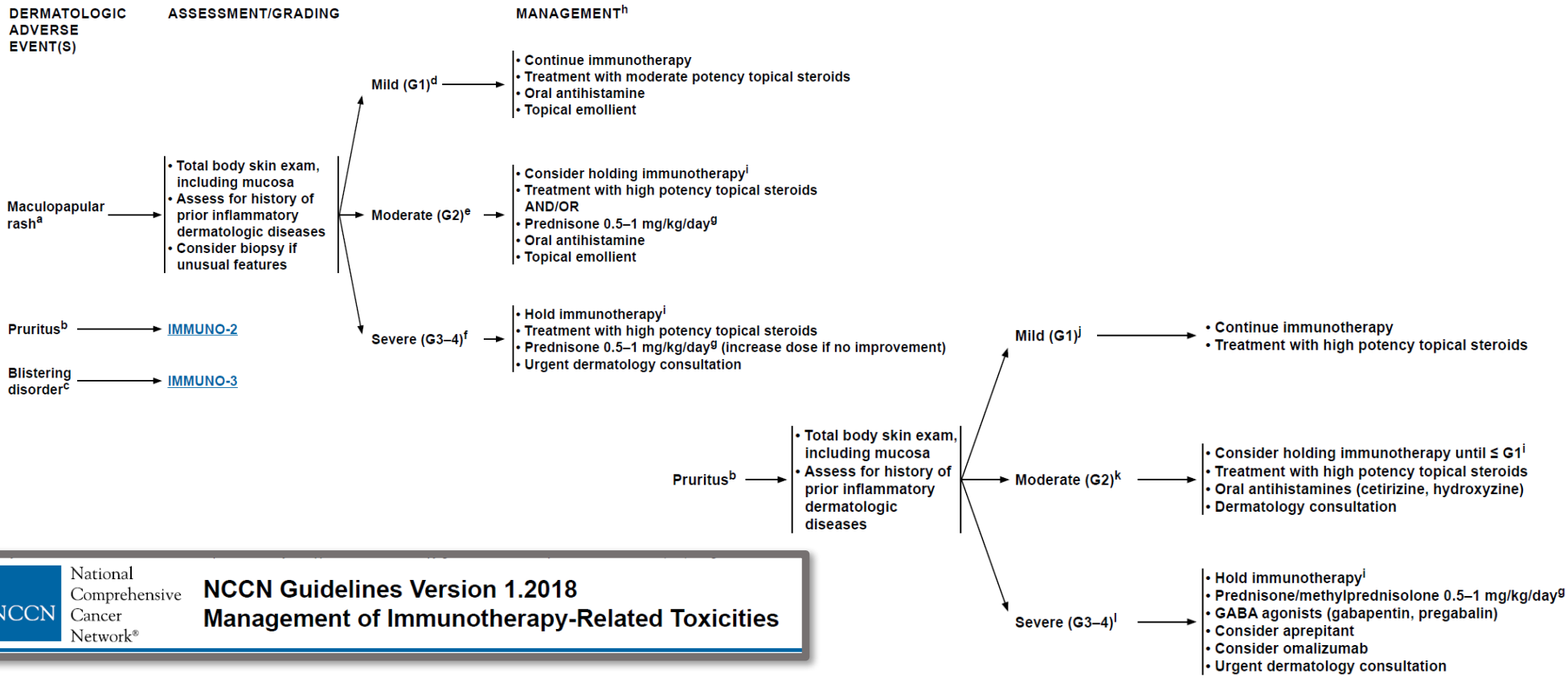
- Symptoms
  - Rash
  - Itching
  - Fevers
  - Skin desquamation and sloughing of oral mucosa in severe cases (Stevens-Johnson syndrome, toxic epidermal necrolysis)
- Workup
  - Generally diagnosed based on appearance
  - Severe or treatment-refractory cases may require biopsy
- Management
  - Grade 1–2 managed with topical corticosteroids and oral antipruritic
    - Evaluate for skin infections before applying topical steroid
  - Grade 3–4 systemic steroid course
    - Consider skin biopsy for histologic classification





Images courtesy Brianna Hoffner, University of Colorado.

Management: Dermatitis



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

Oral Mucosa

- May include mucositis, gingivitis, and sicca (Sjögren) syndrome
- Approximately 5% of patients on checkpoint inhibitors have symptoms of dry mouth[1]
  - More common in anti–PD-1 agents[2]
- Workup
  - ANA
  - SSA/SSB screen
- Management
  - Oral corticosteroid rinses
  - Pilocarpine chlorhydrate
  - Viscous lidocaine
  - Good oral hygiene

ANA = anti-nuclear antibodies; SSA = Sjogren syndrome A; SSB = Sjogren syndrome B.

1. Michot JM, et al. *Eur J Cancer* 2016;54:139-48; 2. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53.

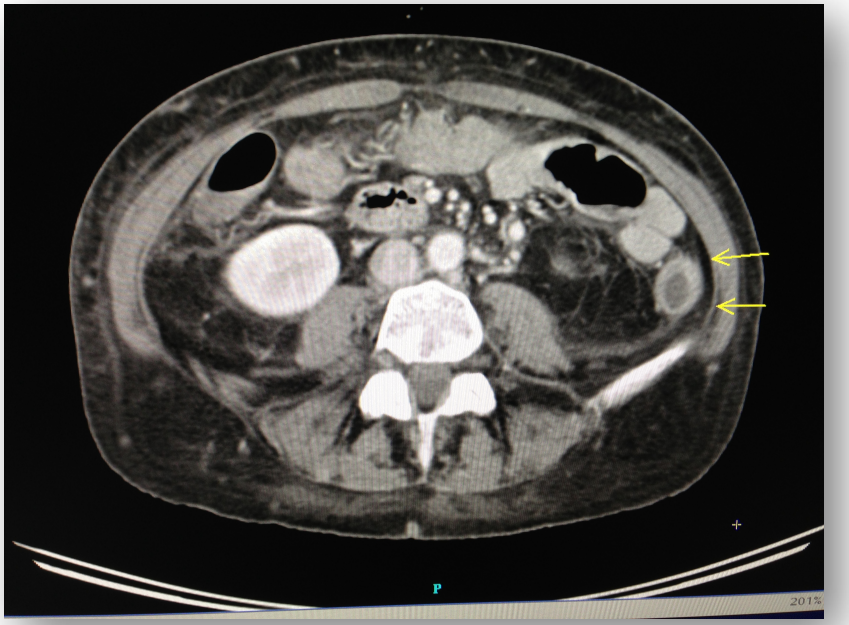
Diarrhea and/or Colitis

- Diarrhea and/or colitis is the most common and potentially most serious complication of anti–CTLA-4 therapy
  - Some trials report up to 31% of patients experiencing some grade of diarrhea, with 6% experiencing severe colitis[1]
  - Bowel perforation, sepsis, and death have been reported
- Grade 3/4 colitis more common in CTLA-4 (7%) than PD-1 (1.8%)[2]
  - Approximately 8% grade 3/4 in combination therapy[3]
- Median time to onset 6–8 weeks in CTLA-4 or CTLA-4/PD-1, longer in PD-1[2]

1. Hodi FS, et l. *N Engl J* Med 2010;363:711-23; 2. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53; 3. Larkin J, et al. *N Engl J Med* 2015;373:23-34.

Diarrhea and/or Colitis (cont.)

- Symptoms
  - Abdominal cramping, pain
  - Anorexia, dyspepsia
  - Diarrhea
  - Blood or mucus in stool
  - Leukocytosis
  - Serum electrolyte abnormalities
  - 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

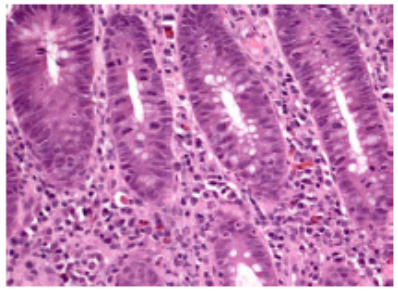


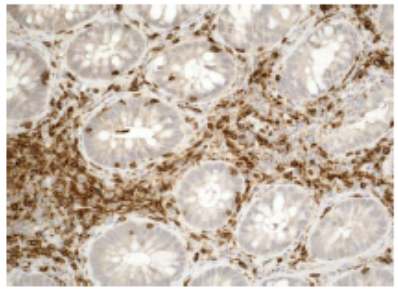
CT = computed tomography.

Image courtesy Brianna Hoffner, University of Colorado.

Diarrhea and/or Colitis (cont.)

- Sigmoidoscopy/colonoscopy may be done if diagnosis is unclear
- Pathologic features resemble Crohn disease
  - Mucosal erythema and ulcerations
  - Histologic patterns include lymphocytic and neutrophil inflammation with cryptitis and, in some cases, crypt abscesses and granuloma

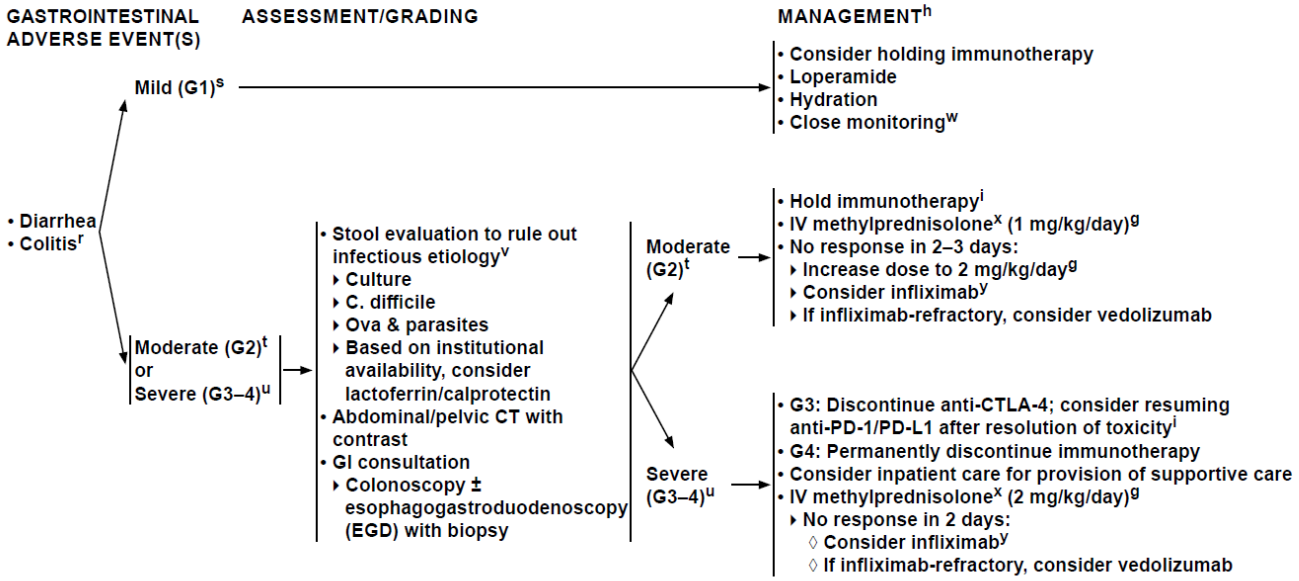




- Prevention with budesonide (oral); randomized phase II trial no benefit shown[1]
- Diarrhea/colitis with one checkpoint inhibitor does not prohibit use of another[2]

1. Weber J, et al. *Clin Cancer Res* 2009;15:5591-8; 2. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53.

Management: Diarrhea or Colitis



[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[r]Symptoms include: abdominal pain, blood and mucus in the stool, fever.
[s]Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
[t]4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[u]More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).
[v]It is not necessary to wait for test results before providing therapy to manage irAE.
[w]If progressive, consider stool evaluation to rule out infectious etiology.
[x]Convert to prednisone when appropriate.
[y]Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers is not clearly defined, but is usually a single dose. Repeat endoscopy may be helpful, but optional for the guidance of treatment.

Endocrinopathies

- Approximately 5%–10% of patients treated with anti–CTLA-4 and anti–PD-1/PD-L1 develop endocrinopathies[1]
- Many endocrine disorders do not resolve, require lifelong replacement
- May include
  - Hypothyroid/hyperthyroid
  - Hypophysitis
  - Adrenal insufficiency
  - Diabetes

1. Michot JM, et al. *Eur J Cancer* 2016;54:139-48.

Thyroid Disorders

- Hypothyroidism most commonly seen with PD-1 (6%)[1]
  - Primary hypothyroidism often preceded by transient hyperthyroidism[2]
  - CTLA-4 approximately 5.6% of patients
  - Many studies did not distinguish between primary thyroid dysfunction (related to thyroid gland dysfunction) and secondary thyroid dysfunction (due to hypophysitis-related pituitary dysfunction)
- Evaluation
  - 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.

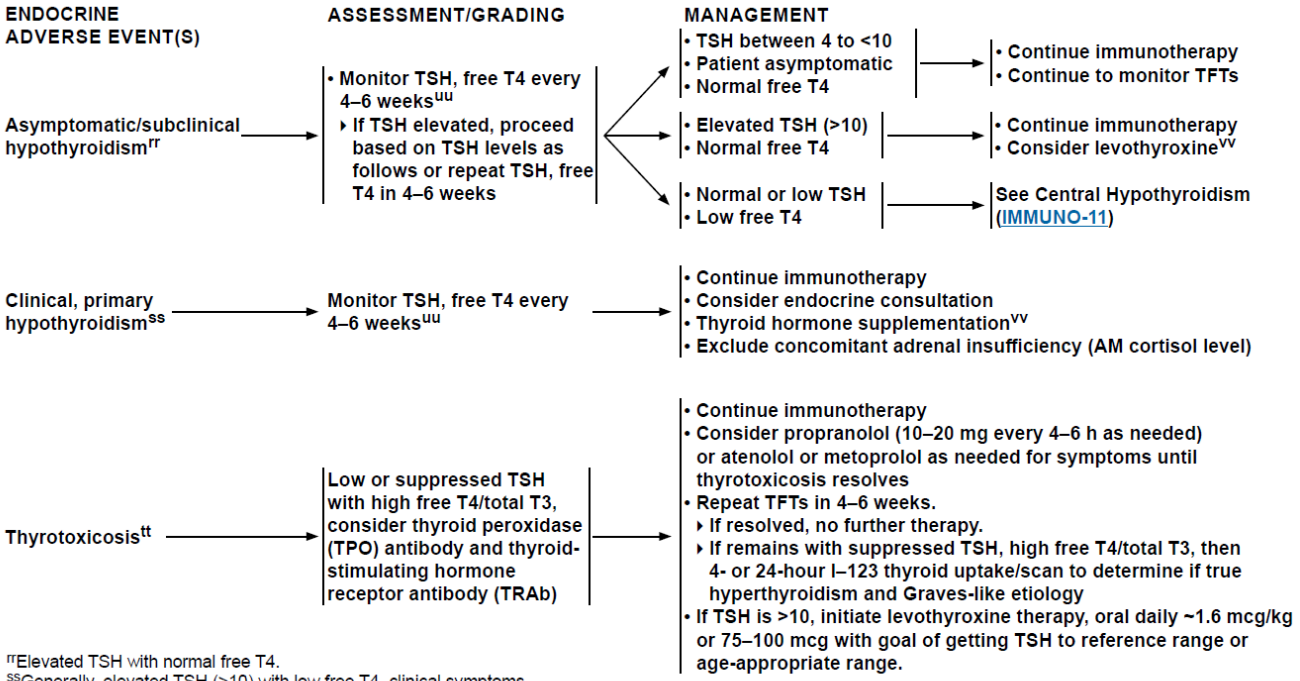
1. Merck, Pembrolizumab PI, 2014, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf; 2. Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207.

Thyroid Disorders (cont.)

- Mechanism
  - CTLA-4: polymorphisms in CTLA-4 may lead to higher incidence
  - PD-1: unclear but may also be related to polymorphisms in PD-1 gene
- Management
  - Thyrotoxicosis
    - Supportive beta-blockers
    - Hold immunotherapy
    - Radioactive iodine uptake generally inaccurate
    - Generally self-limiting
    - Monitor for subsequent hypothyroidism
  - Hypothyroidism
    - Hormone replacement

Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207.

Management: Thyroiditis



[rr]Elevated TSH with normal free T4.
[ss]Generally, elevated TSH (>10) with low free T4, clinical symptoms.
[tt]Defined as suppressed TSH that may be: a) subclinical if free T4 normal, b) clinical if high free T4. The majority of suppressed TSH (<0.01) are due to transient or progressive painless thyroiditis.
[uu]For patients without baseline thyroid function abnormalities or who are asymptomatic, can increase thyroid function testing interval to every 12–18 weeks as indicated.
[vv]Levothyroxine oral daily ~1.6 mcg/kg with goal of getting TSH to reference range or age-appropriate range; reduce dose by 10% to avoid hyperthyroidism in patient populations that may be sensitive to thyroid supplementation (eg, elderly populations or patients with comorbidities).

Hypophysitis

- Inflammation of the pituitary resulting in low release of all or some of the following pituitary hormones
  - ACTH
  - TSH
  - FSH
  - LH
  - Growth hormone (prolactin)
- Symptoms
  - Headache
  - Fatigue
  - Muscle weakness
  - Constipation
  - Cognitive difficulties (related to thyrotropin axis)
  - Erectile dysfunction/amenorrhea (gonadotropin axis, LH/FSH)
  - Orthostatic hypotension, hypoglycemia/hyponatremia (corticotrophin deficiency, ACTH)

Michot JM, et al. *Eur J Cancer* 2016;54:139-48.

Hypophysitis (cont.)

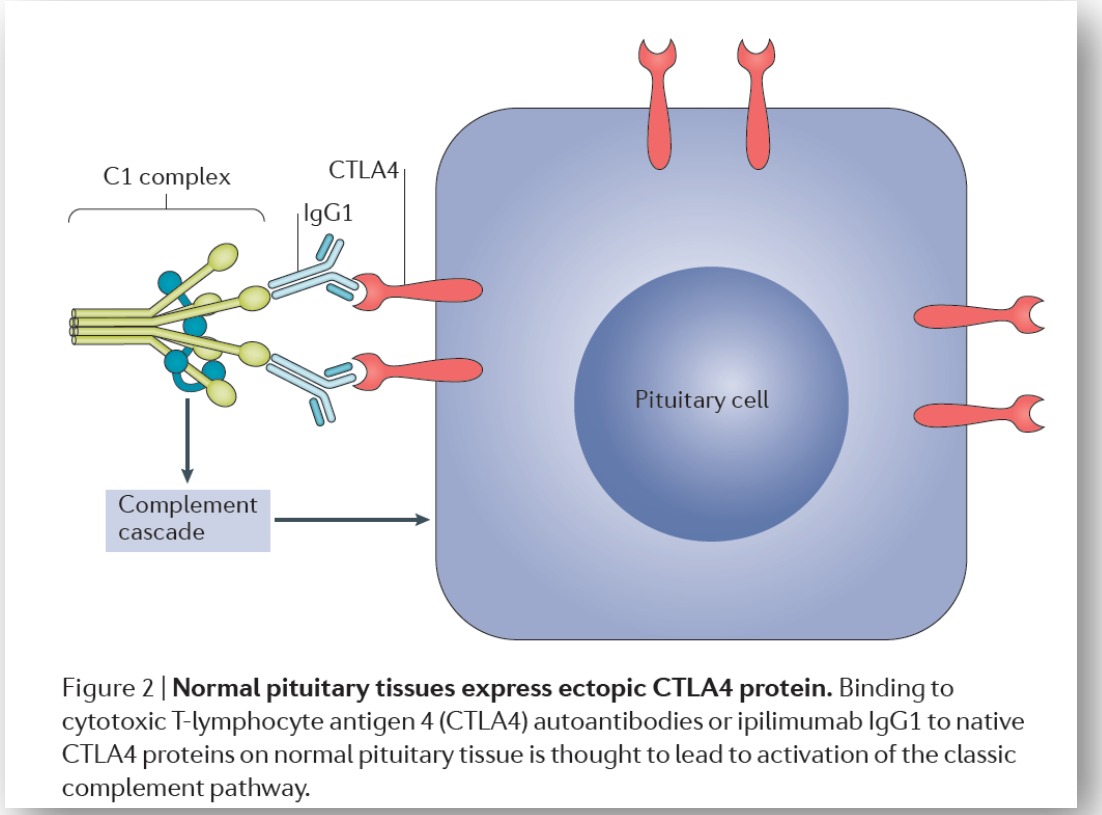


Figure 2 | **Normal pituitary tissues express ectopic CTLA4 protein.** Binding to cytotoxic T-lymphocyte antigen 4 (CTLA4) autoantibodies or ipilimumab IgG1 to native CTLA4 proteins on normal pituitary tissue is thought to lead to activation of the classic complement pathway.

Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207.

Hypophysitis (cont.)

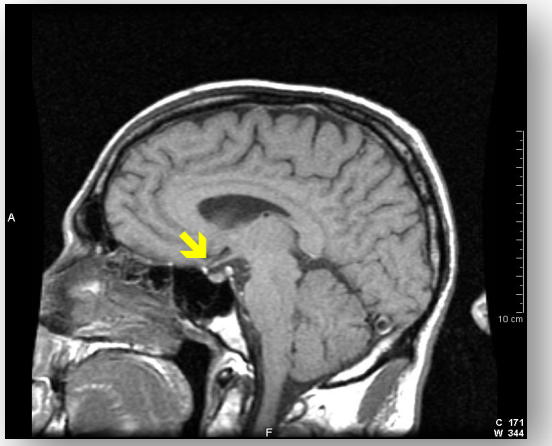
- Most common with anti–CTLA-4[1]
  - Incidence ranging from 0.4%–17%[1]
    - Wide range may be due to dose level, hormonal monitoring, and improved recognition[1]
- Ipilimumab + PD-1 incidence approximately 9%[1]
- Can lead to secondary hypothyroidism (7.6%), secondary adrenal insufficiency (6.1%), and secondary hypogonadism (7.5%)
- Time to onset approximately 6–12 weeks
- May be more common in men than women
- Treatment
  - High-dose steroid for critical illness
  - Low-dose glucocorticoid to alleviate headache/fatigue
  - Replace pituitary hormone deficiencies (start with adrenal insufficiency)

1. Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207.

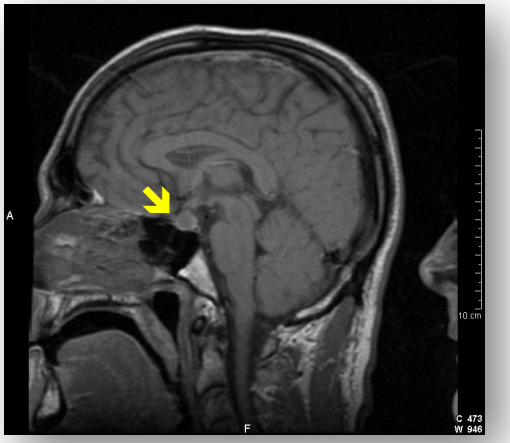
Hypophysitis (cont.)

Workup

- Evaluation of pituitary gland hormones (ACTH, TSH, FSH, LH, prolactin, cortisol)
- MRI brain with contrast (pituitary cuts)



Pre-ipilimumab

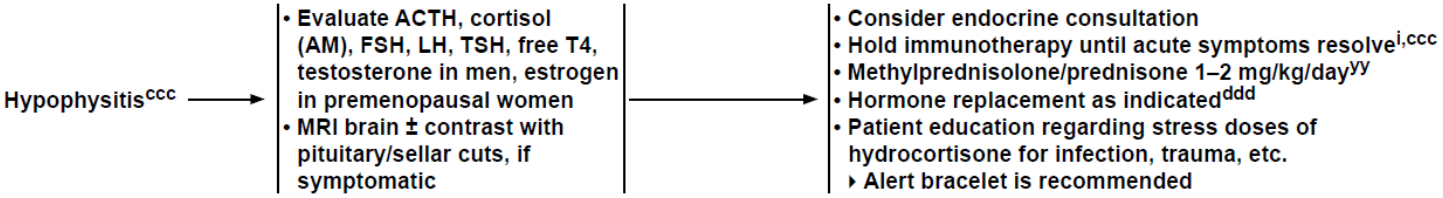


Post-ipilimumab

MRI = magnetic resonance imaging.

Images courtesy Brianna Hoffner, University of Colorado.

Management: Hypophysitis



[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[yy]If severe acute symptoms (eg, headache/nausea/emesis, fevers), high-dose steroids as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement.
[ccc]Hypophysitis may present with acute symptoms such as headache, photophobia, dizziness, nausea/emesis, fevers, or anorexia. Tests may show low ACTH, low AM cortisol, low Na, low K, low testosterone, and DHEA-S. Non-acute symptoms may include fatigue and possible weight loss.
[ddd]Hormone replacement for pituitary damage should include steroid replacement (hydrocortisone 20 mg PO every AM, 10 mg PO every PM); it may also include levothyroxine for central hypothyroidism and testosterone supplementation in males. Patients may require physiologic replacement hormones indefinitely.

Diabetes Mellitus

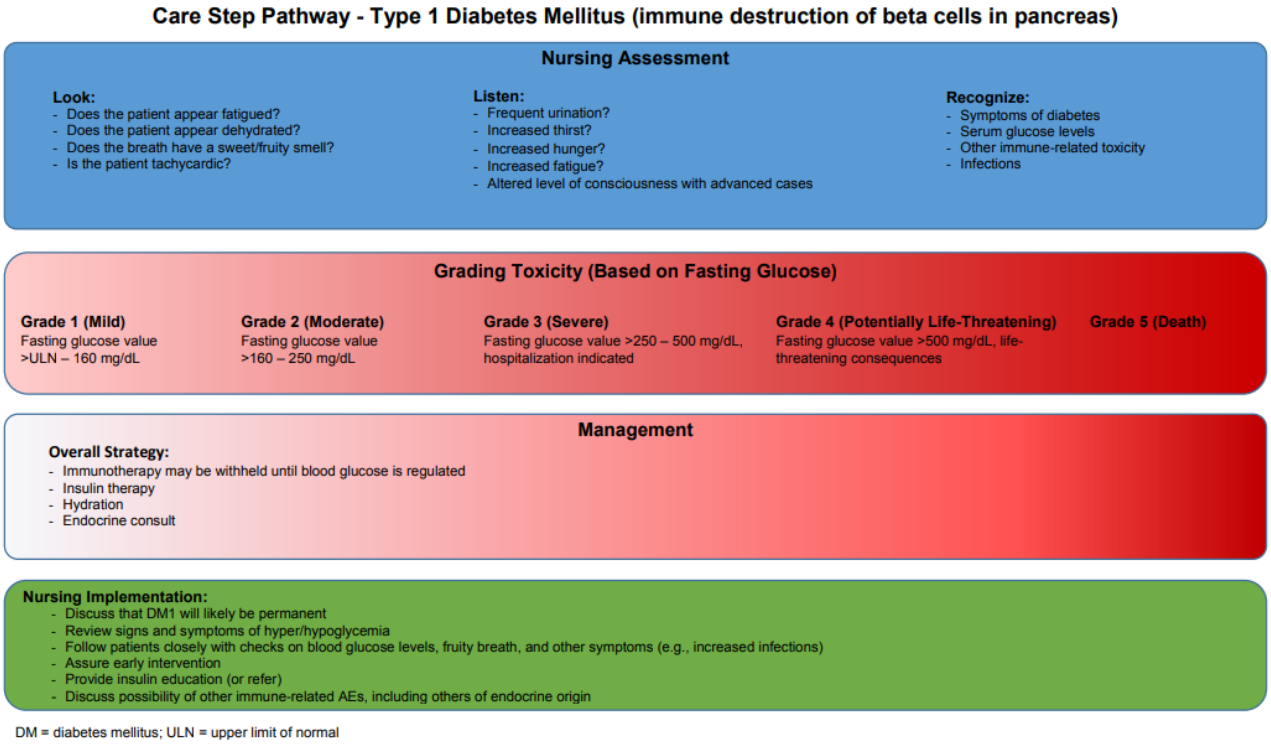
- Rare occurrence with PD-1
- Patients generally present in DKA[1]
- Workup should include testing for GAD65 antibodies
- Mechanism unclear[1]
  - In one study, 2 of 5 patients presented with upregulation of CD8+ T-cell response to a T1DM antigen
  - 3 of 5 patients were found to have GAD65 antibodies
- Treatment with insulin therapy

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

1. Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207.

Management: DM1

Look, Listen, Recognize



Grading

Management (by grade when applicable)

Implementation Tips

Adrenalitis

- Primary adrenal insufficiency extremely rare but reported with CTLA-4
- Adrenal gland enlargement can be seen on CT scans
- Workup
  - ACTH
  - Cortisol
  - Cosyntropin stimulation test
- Management
  - Replacement with oral hydrocortisone

Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207.

Management: Adrenalitis

ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[h,yy]
Primary Adrenal Insufficiency[ww]	• Evaluate ACTH, cortisol level (AM) • Comprehensive metabolic panel (Na, K, CO_2, glucose), renin level	• Endocrine consultation ‣ Endocrine evaluation prior to surgery or any procedure • Hold immunotherapy[i] • Start corticosteroid first before other hormone replacement to avoid adrenal crisis • Steroid replacement[zz,aaa] ‣ Hydrocortisone 20 mg in AM, 10 mg in PM, then slowly titrating doses down according to symptoms[bbb] OR ‣ Prednisone 7.5- or 10-mg starting dose, then reduce to 5 mg daily as appropriate AND ‣ Fludrocortisone can be started 0.1 mg every other day; then titrated up or down by BPs, symptoms, lower extremity edema, and labs • If hemodynamically unstable, inpatient care and initiate high-dose/stress-dose steroids • Patients with severe symptoms (hypotension) may require additional fluids (eg, normal saline often >2 L required) • Patient education regarding stress doses of hydrocortisone for infection, trauma, etc. ‣ Alert bracelet is recommended

[ww]Low morning cortisol (<5) with high ACTH (> reference range) with or without abnormal electrolytes and symptoms. Other criteria: 30- or 60-minute cortisol <18 after ACTH stimulation in the setting of low morning cortisol and high ACTH. Other abnormalities: hypotension, orthostatic hypotension, low Na, and high K.

Pneumonitis

- Occurs in approximately 1%–2% of patients treated with PD-1 and/or CTLA-4[1,2]
- Time to onset 9–19 weeks (earlier with nivolumab than pembrolizumab)[2]
- Symptoms
  - Dry, unproductive cough
  - Dyspnea
  - Cyanosis (late)
  - Fatigue
- Differential diagnosis
  - Infection
  - Allergies
  - Cardiac causes (myocarditis)
- Late diagnosis may lead to chronic, irreversible lung disease[2]

1. Michot JM, et al. *Eur J Cancer* 2016;54:139-48; 2. Eigentler TK, et al. *Cancer Treat Rev* 2016;45:7-18.

Pneumonitis (cont.)

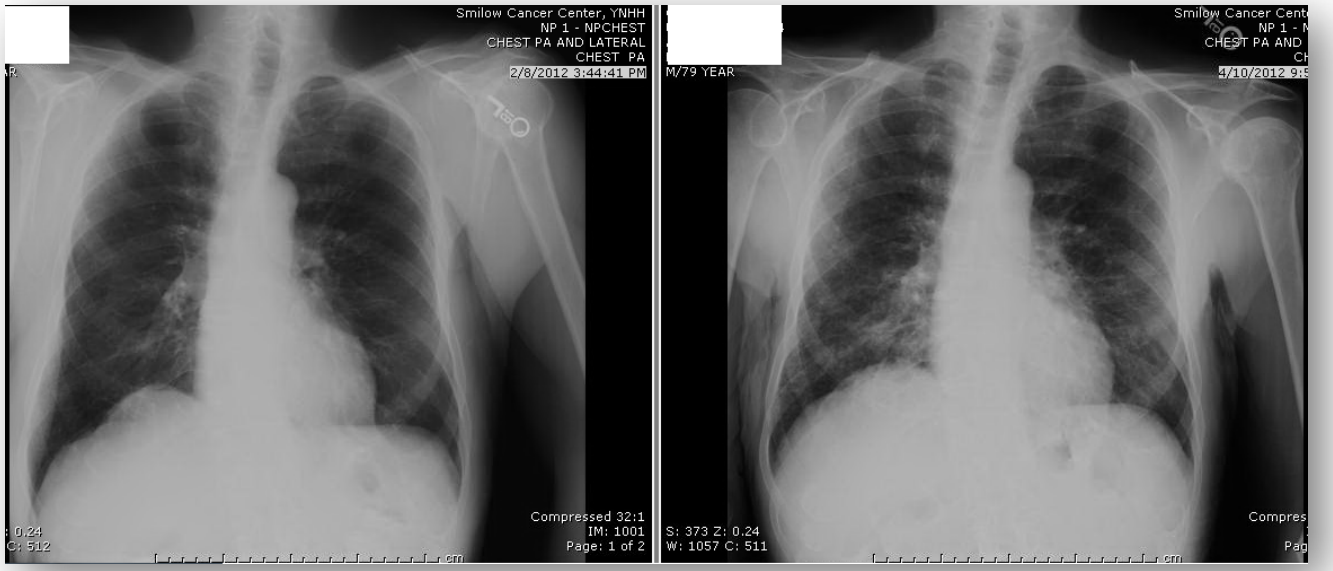
- Workup
  - Chest x-rat and/or CT scan
    - Radiographic findings of ground-glass lesions and/or disseminated nodular infiltrates
  - Bronchoscopy
  - PFT
  - Blood gas
- Treatment
  - Steroid therapy (guided by radiographic/symptomatic response)
  - Prophylactic antibiotic/antifungal therapy during high-dose steroid
  - Mycophenolate mofetil, cyclophosphamide, IVIG, or infliximab in severe cases[1,2]

PFT = pulmonary function testing.

1. Eigentler TK, et al. *Cancer Treat Rev* 2016;45:7-18; 2. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53.

Pneumonitis (cont.)

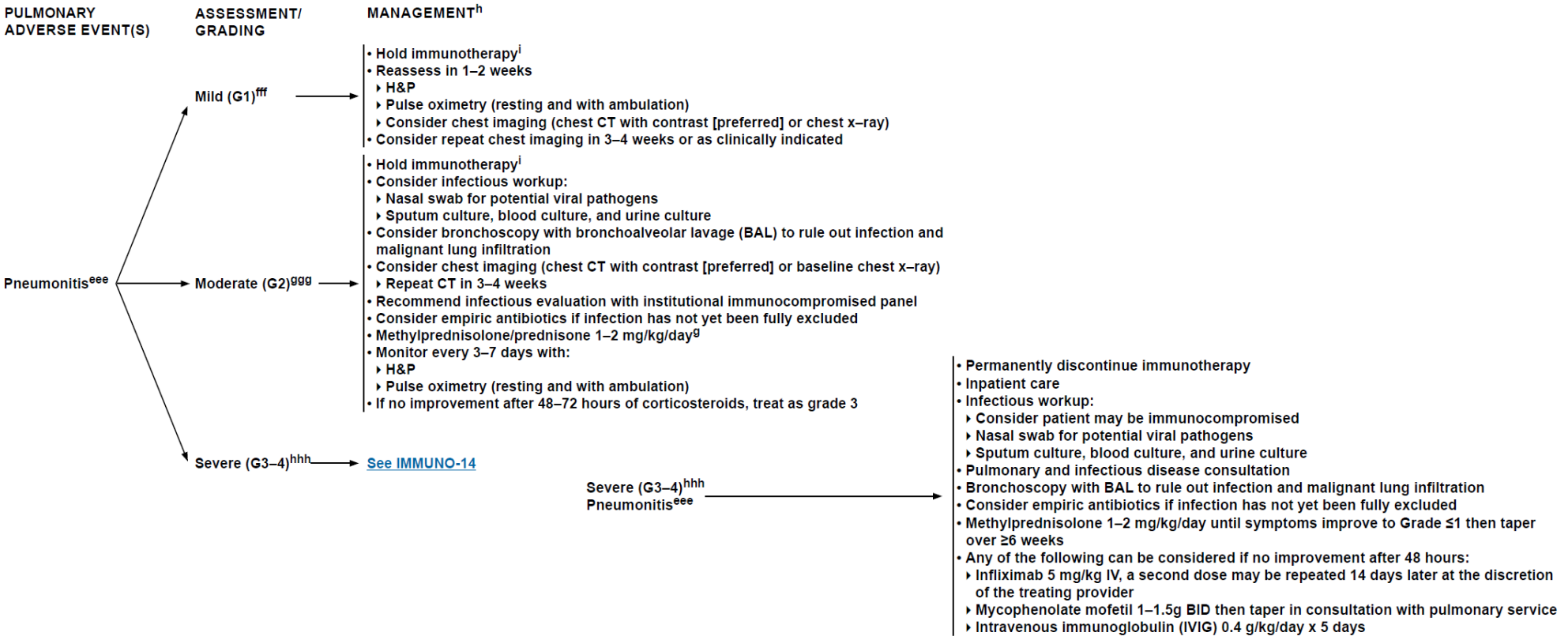
CXR showing increased interstitial markings compared with baseline



Baseline **After two doses PD-1/CTLA-4**

Images courtesy Matthew Burke, Smilow Cancer Center.

Management: Pneumonitis



Hepatitis

- Incidence
  - Less common than colitis, seen in 2%–9% of patients, and at least 1 death has been reported on anti–CTLA-4 therapy alone[1]
  - Incidence with anti–PD-1 closer to 0.5%[2]
  - Hepatotoxicity appears worse when ipilimumab combined other drugs including dacarbazine[3] and vemurafenib[4]
  - Combination therapy 15%–18% overall and 6%–8% grade 3/4[5]
- Time to onset 8–12 weeks in single agent, sooner in combination[6]
- Symptoms
  - Abdominal bloating or pain, dyspepsia, jaundice, and nausea
  - Usually asymptomatic and diagnosed based on elevated LFT[6]

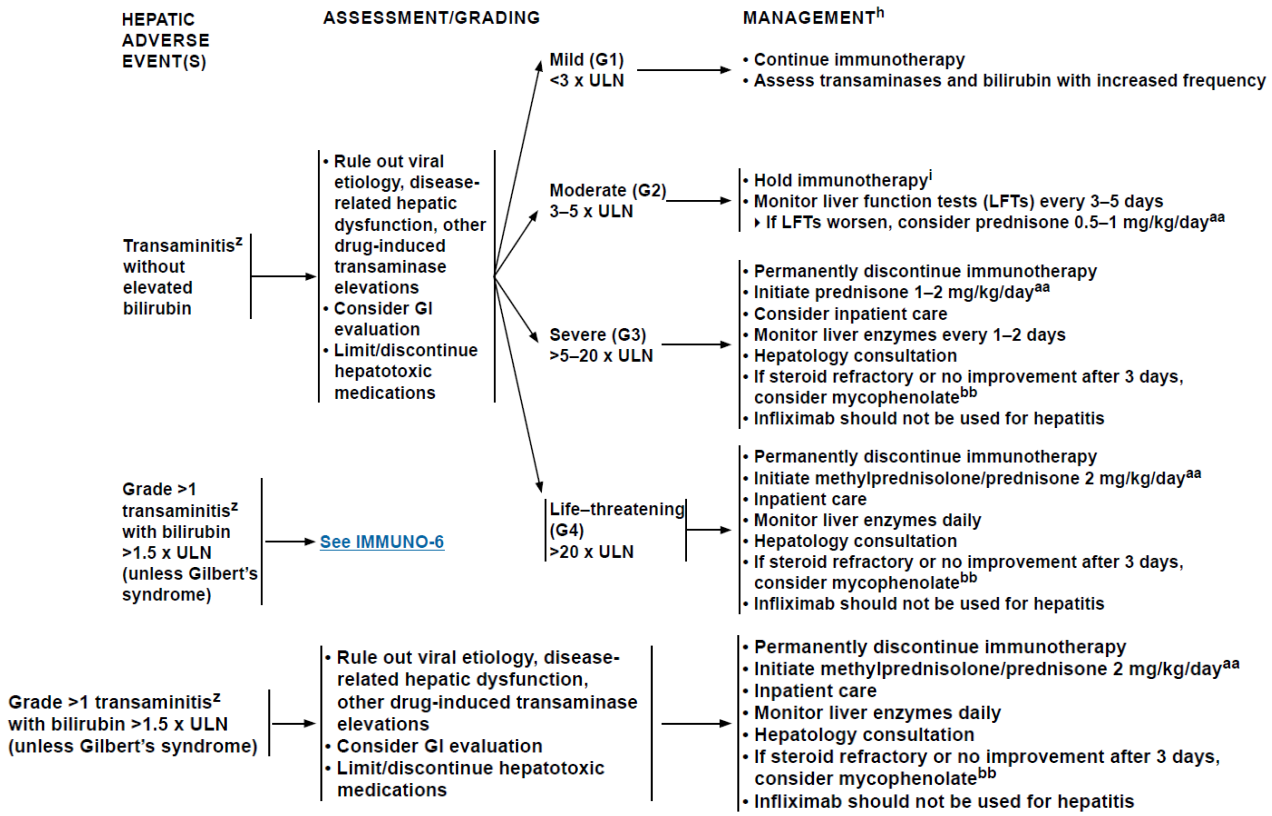
1. Hodi FS, et l. *N Engl J* Med 2010;363:711-23; 2. Merck, Pembrolizumab PI, 2014, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf; 3. Robert C, et al. *N Engl J Med* 2011;364:2517-26; 4. Ribas A, et al. *N Engl J Med* 2013;368:1365-6; 5. Larkin J, et al. *N Engl J Med* 2015;373:23-43; 6. Friedman CF, et al. *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
    - Patients with hepatitis may have mild hepatomegaly on imaging[1]
  - Biopsy (if needed)
    - Diffuse T-cell infiltrate seen on pathology with diagnosis of hepatitis[1]
- 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

1. Michot JM, et al. *Eur J Cancer* 2016;54:139-48; 2. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53.

Management: Hepatitis



Hepatitis in HCC

- Literature review of clinical trials that have been completed with single agent immune checkpoint inhibitors for patients with HCC, melanoma, and NSCLC
  - Evaluation of gastrointestinal related adverse events including elevation of AST, ALT, and diarrhea
- Demonstrated that patients with HCC treated with immune checkpoint inhibitors have a substantial increase in AST/ALT compared to melanoma/NSCLC, but this does not cause patients to come off therapy or cause death secondary to drug toxicity

Table 2 Total adverse events reported per cancer

Disease	Number of Patients	Taken off therapy secondary to toxicity	Death secondary to toxicity	Elevation AST any grade	Elevation AST grade 3–4	Elevation ALT any grade	Elevation ALT grade 3–4	Diarrhea any grade	Diarrhea grade 3–4
HCC	314	16	0	51	30	41	16	40	4
NSCLC	1866	75	10	43	6	47	5	161	22
Melanoma	4118	548	21	156	33	179	38	1242	320

HCC Hepatocellular Carcinoma, *NSCLC* Non-small cell lung cancer, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

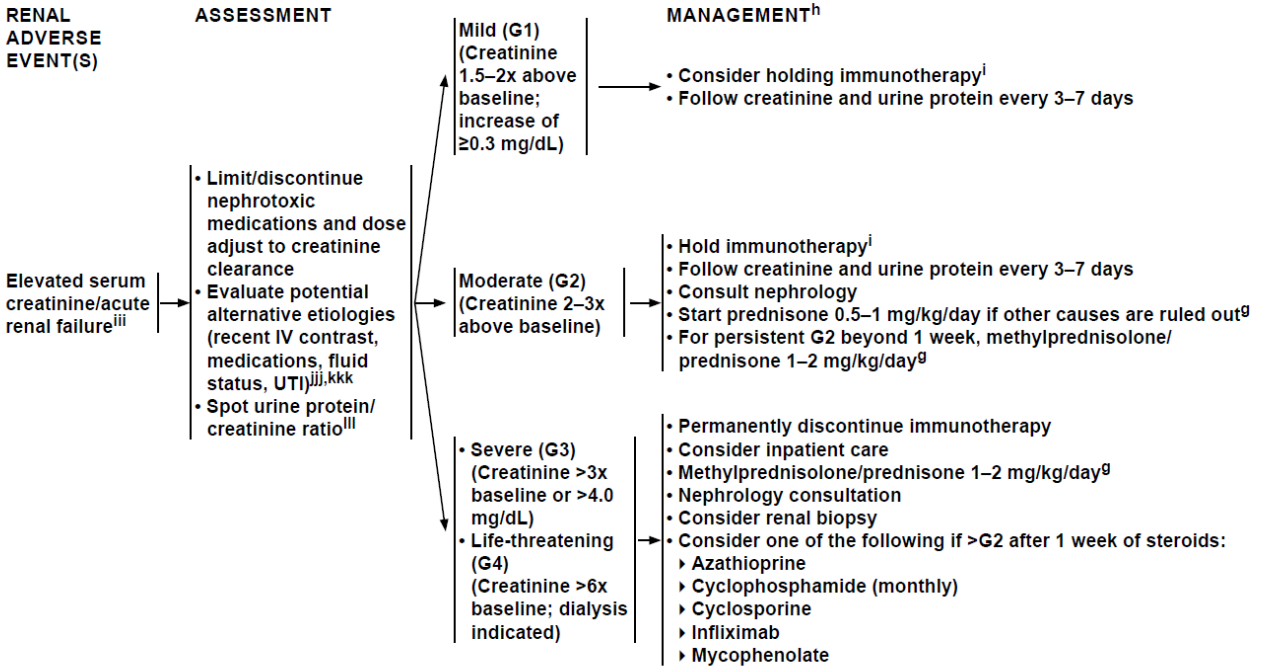
Nephritis

- Seen in approximately 1% of patients on checkpoint inhibitor therapy[1]
- Includes
  - Interstitial nephritis with inflammatory cortical renal enlargement
  - Granulomatous nephritis
  - Glomerular lupus-like nephropathy
- Median time to onset variable (6–30 weeks)[2]
- Diagnosis to include CMP, urine studies, renal biopsy if needed
- Treatment with steroid

CMP = comprehensive metabolic panel.

1. Michot JM, et al. *Eur J Cancer* 2016;54:139-48; 2. Eigentler TK, et al. *Cancer Treat Rev* 2016;45:7-18.

Management: Nephritis



[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[iii]Azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, and urine output change.
[jjj]General medical review and testing as warranted for prerenal and postrenal causes. Include medication review for nephrotoxic agents such as NSAIDS, consider obstruction, cardiomyopathy/heart failure, pulmonary hypertension, diuretics, hypovolemia due to primary GI cause, stones, and infection.
[kkk]Distinguish cell infiltrate vs immune-complex mediated renal injury.
[lll]For proteinuria >3 g/24-hour check ANA, RF, ANCA, anti-dsDNA, and serum C3, C4, and CH50.

Other irAEs

Pancreatic

- Asymptomatic elevation in amylase/lipase
- Pancreatitis
  - Radiographic findings of an inflamed pancreas, elevated amylase/lipase, clinical symptoms
- Clinical relevance of asymptomatic elevations remains unclear[1]
- Management algorithms included in NCCN Guidelines

1. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53.

Neurologic

- Less than 5% of patients receiving checkpoint inhibitors1
- Includes
  - Neuropathies
  - Aseptic meningitis
  - Temporal arteritis
  - Myasthenia gravis
  - Guillain-Barré syndrome
- Treatment with steroid not universally effective
  - May need intravenous immunoglobulin (IVIG)

1. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53.

Neurologic (cont.)

Table 6. Typical workup for patients with new-onset neurologic findings

Test	Consideration
Measure pituitary axes/thyroid panel	Hypophysitis
Lumbar puncture	Infectious etiologies
Lumbar puncture for cytopathology	Leptomeningeal disease
Brain MRI	Stroke/ischemia; brain metastases
EEG monitoring (spot as well as 24 hour)	Subclinical seizures
Toxicity screen	Systemic infections, e.g., metabolic causes
Blood and cerebrospinal fluid paraneoplastic panel	Paraneoplastic causes

Abbreviations: EEG, electroencephalogram; MRI, magnetic resonance imaging.

Neurologic (cont.)

- Database search of 3,763 patients with advanced melanoma receiving nivolumab with or without ipilimumab
  - 35 (0.93%) presented with 43 serious neurologic irAEs
  - Most neurologic irAEs resolved (26/35 patients; 75%)
  - Median time to onset was 45 days (range, 1–170)
    - Median time to onset of encephalitis was 55.5 days (range, 18–297)
  - Median time to resolution was 32 days (range, 2–809+)

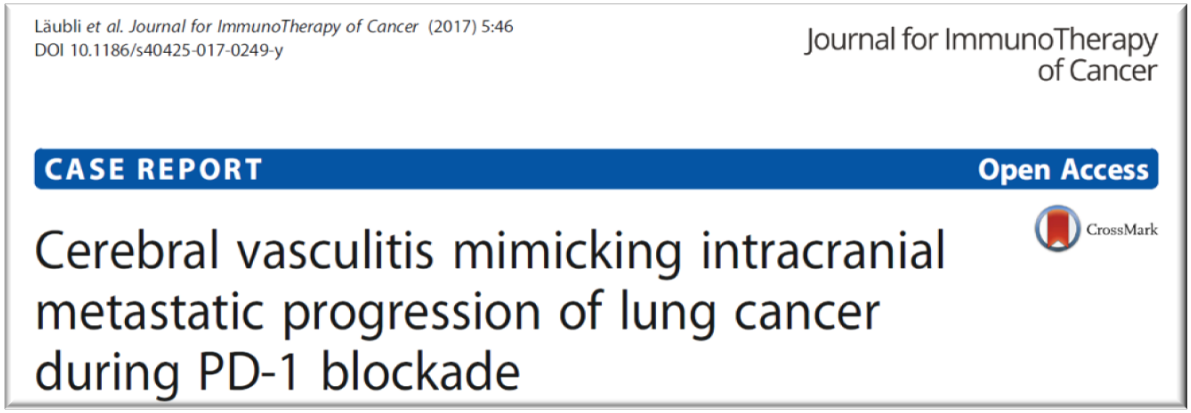
Larkin, J., et al. (2017). Neurologic serious adverse events associated with nivolumab plus ipilimumab or nivolumab alone in advanced melanoma, including a case series of encephalitis. *The Oncologist*, 22, 709-718

Rheumatologic

- Polyarthritis/arthralgia[1]
  - Seen in approximately 5% of patients
  - Reported cases erythematous lupus or polymyalgia rheumatic
  - ANA and anti-cyclic citrullinated peptide to detect autoimmune condition
  - Low-dose oral steroid to control joint manifestations
- Retrospective literature review of rheumatologic irAE noting[2]
  - Arthralgia prevalence in clinical trials 1%–43%
  - Myalgia incidence 2%–20%
  - Arthritis reported in 5 of 33 clinical trials
  - Vasculitis reported in 2 clinical trials

1. Michot JM, et al. *Eur J Cancer* 2016;54:139-48; 2. Cappelli, L.C., et al. (2017). Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care and Research, 69(11), 1751-1763

Rheumatologic (cont.)


Läubli et al. Journal for ImmunoTherapy of Cancer (2017) 5:46
DOI 10.1186/s40425-017-0249-y

Journal for ImmunoTherapy of Cancer

CASE REPORT Open Access

Cerebral vasculitis mimicking intracranial metastatic progression of lung cancer during PD-1 blockade

- Metastatic adenocarcinoma patient treated with PD-1
- Developed cerebral lesions while having disease stabilization of extracranial metastases
- Lesion progressed despite stereotactic irradiation
- Resected specimen showed cerebral vasculitis, no cancer
- +ANA and anti-vascular endothelial antibodies in serum

Rheumatologic (cont.)

- Adjuvant ipilimumab administration in resected stage IIIB/C melanoma patient
- Developed discoloration of upper/lower limb digits after second ipilimumab 10 mg/kg dose → thought to be Raynaud's
  - Serologic workup negative
- This patient received high-dose steroids, 5-day IV epoprostenol protocol, botulinum toxin injections, and rituximab at 375 mg/m^2 weekly for 4 cycles
- With this treatment regimen, the digital ischemia did not progress proximally, but she did require multiple distal digit amputations about 6 months after the onset of her symptoms

CASE REPORT

Ipilimumab induced digital vasculitis

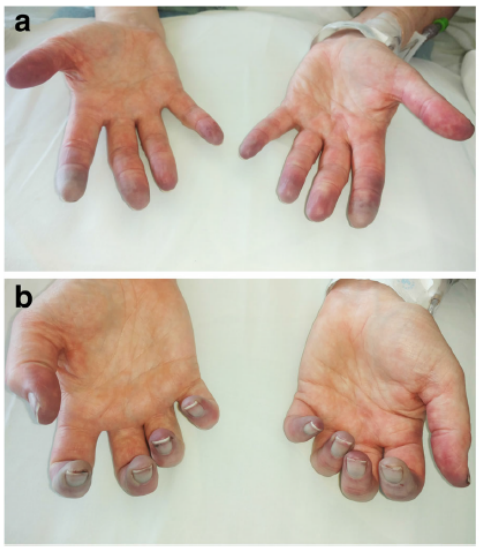


Fig. 1 (Panel **a** and **b**). This picture was taken four weeks after her second Ipilimumab infusion (week 26 on timeline). Physical exam reveals acrocyanosis of all digits with small ulcers of the right second and fourth fingertips

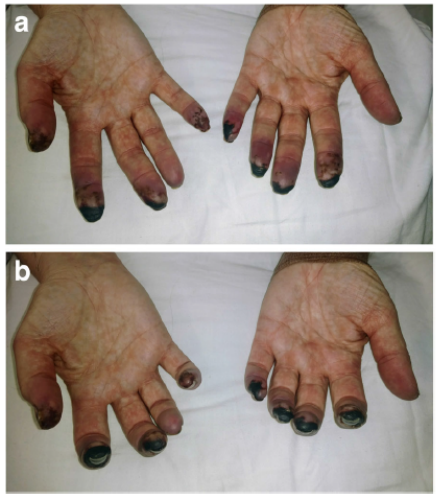


Fig. 3 (Panel **a** and **b**) This picture was taken nine weeks after her second Ipilimumab infusion (week 31 on timeline). The patient is status-post high dose steroids and four cycles of Rituximab. The exam appeared worse with dry gangrene of the fingertips, secondary to the natural evolution of skin changes with distal digital ischemia. We believe that the vasculitic process was halted, as she did not develop further proximal digital ischemia

Serum Auto-Antibodies

Serum auto-antibody assays with potential value for identifying IRAEs.

Immune-related organ involved		Antibodies
Gastro-intestinal		None
Liver		Antinuclear antibodies (ANAs)
		Anti-smooth muscle, anti-liver kidney microsomal antibody type 1, anti-liver cytosol type 1
Lung		Antinuclear antibodies (ANAs)
		Rheumatoid factor
		Anti-centromere
		Extractable nuclear antigens (ENA): anti-Sm, anti-RNP; anti-Ro (SSA), anti-La (SSB); anti-Scl70, anti-Jo
Endocrine	Thyroid	Anti-thyroglobulin and anti-TPO
	Diabetes mellitus	Anti-GAD, anti-insulin, anti-carbonic anhydrase
	Addison's disease	Anti-21 hydroxylase
	Hypophysitis	Anti-pituitary
Skin		None
Polyarthritis		Antinuclear antibodies (ANAs)
		Anti-ENA: Anti-SSA, SSB, Sm
		Anti-CCP, complement fractions C3 C4 CH50
Renal		Antinuclear antibodies (ANAs)
		Complement fractions C3 C4 CH50
		Anti-neutrophil cytoplasmic (ANCA)
Haematologic syndromes		Antinuclear antibodies (ANAs)
		Coombs' erythrocyte test

IRAEs = immune-related adverse events; CCP = cyclic citrullinated peptide; GAD = Glutamate decarboxylase; RNP = ribonucleoprotein; Sm = Small nuclear ribonucleoprotein; SSA = Sjogren's syndrome-related antigen A; Scl = Sclerosis systemic; SSB = Sjogren's syndrome-related antigen B; TPO = Thyroid peroxidase.

Hematologic

Hematologic toxicity[1]

- Anemia described in < 5% CTLA-4 and < 10% PD-1[2]
- Red cell aplasia, autoimmune neutropenia, pancytopenia, acquired hemophilia A also reported[1]
- Workup to include peripheral smear, reticulocyte count, Coombs test, hemolysis assays, and bone marrow biopsy[1]

Table 1. Patient Workup after Three Doses of Anti–Programmed Death 1 Antibody.

Marker or Test	Value or Finding	Normal Range or Normal Finding
Hemoglobin — g/dl*	6.3	11.5–14.5
Indirect bilirubin — mg/dl	1.8	0.2–0.7
Haptoglobin — mg/dl	<8	34–200
Lactate dehydrogenase — U/liter	1266	100–250
C-reactive protein — mg/liter	10.3	<7
Erythrocyte sedimentation rate — mm/hr	52	0–30
Direct antiglobulin test	Positive for warm antibodies (reactions with anti-IgG and polyspecific antihuman globulin reagents and not with anti-C3b reagents)	Negative
Reticulocyte count — %	0.1	0.8–2.5
IgG and IgM antibodies for parvovirus B19	Negative	Negative
Peripheral-blood tests	Marked anemia with anisocytosis and absence of polychromasia; white-cell and platelet counts within normal range	Normal morphology
Computed tomography of chest to rule out thymoma	No evidence of mediastinal mass	Absence of mediastinal mass
Bone marrow biopsy	Marked erythroid hypoplasia with maturation arrest; staining for CD71 showed rare erythroid islands; numerous T cells were positive for CD3; staining for CD20 showed rare B lymphocytes	Normal morphology

* The hemoglobin level at baseline was 12.5 g per deciliter.

Example workup for melanoma patient who developed hemolytic anemia on pembrolizumab[2]

1. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53; 2. Nair, R., et al. *N Engl J Med*, 2016;374(11).

Cardiac

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

- Two patients with melanoma who developed fatal myocarditis after treatment with ipilimumab and nivolumab
  - Myositis with rhabdomyolysis
  - Early progressive and refractory cardiac electrical instability
- Myocarditis with robust presence of T-cell and macrophage infiltrates
- Pharmacovigilance studies showing that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab

Johnson, DB, et al. *N Engl J Med* 2016; 375:1749-1755 DOI: 10.1056/NEJMoa1609214

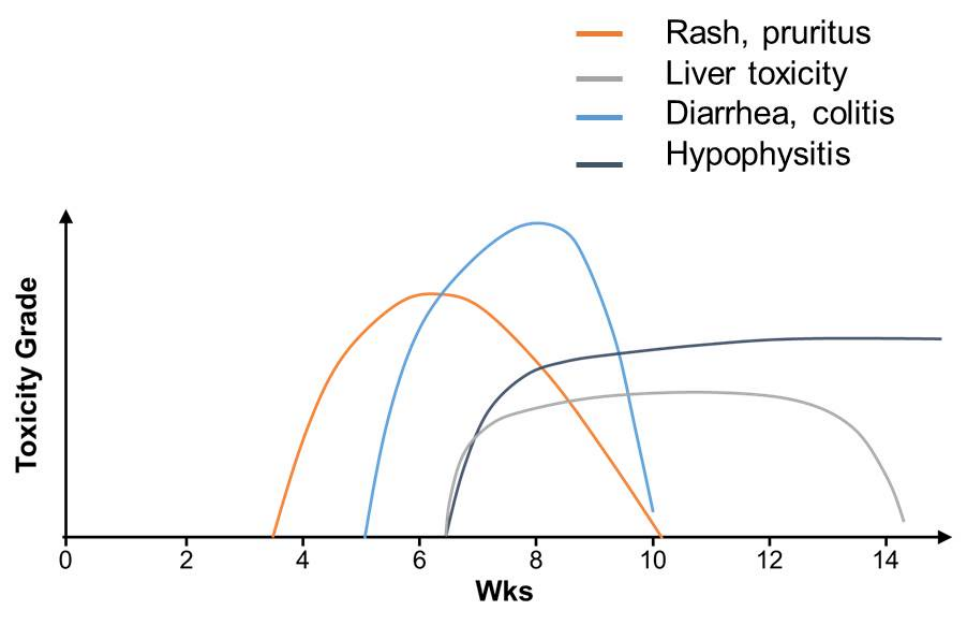
Cardiac (cont.)

- Patient diagnosed with myocarditis based on acute rise in serum cardiac troponin I beginning 2 weeks after initial dose of ipilimumab/nivolumab.
  - Initial presenting symptom was intractable nausea
- Treated with high-dose steroid with rapid resolution of nausea and 4-fold decrease in troponin I over 4 days.
- Serum troponin spiked to 13 x ULN following steroid taper
  - Endomyocardial biopsy with collagen fibrosis and lymphocytic inflammation predominantly comprised of CD*+ T cells
- Chronic prednisone + IVIG

IVIG = intravenous immunoglobulin.

Timing of irAEs

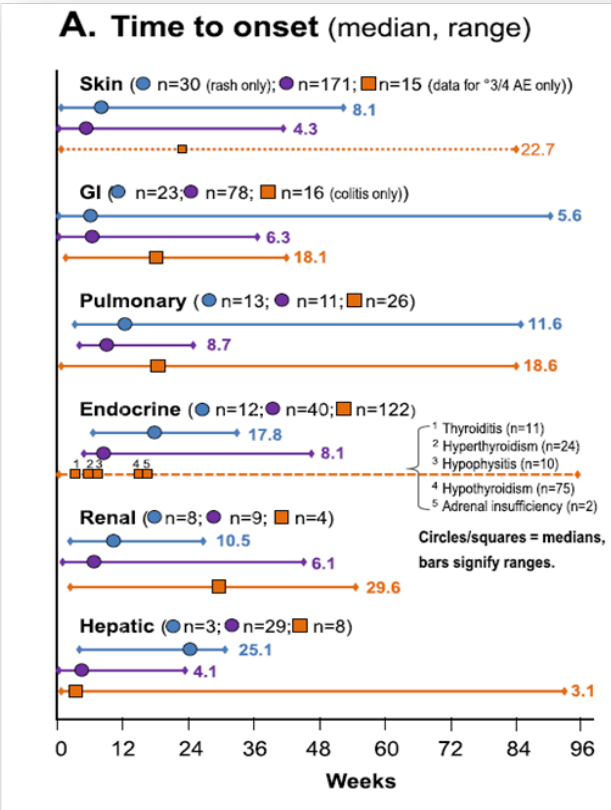
- Loss of self-tolerance
  - Self-reactive T cells may proliferate and react with normal tissue when immune homeostasis or immune tolerance is disrupted
- irAEs can affect one or several organ systems
- Average time to onset
  - 6–12 weeks after initiation of therapy
- May occur within days or may occur months after therapy
  - Skin: after 2–3 weeks
  - GI: after 5–6 weeks
  - Hepatic: after 6–7 weeks
  - Endocrine: after 8–9 weeks
  - irAEs are rare after 24 weeks

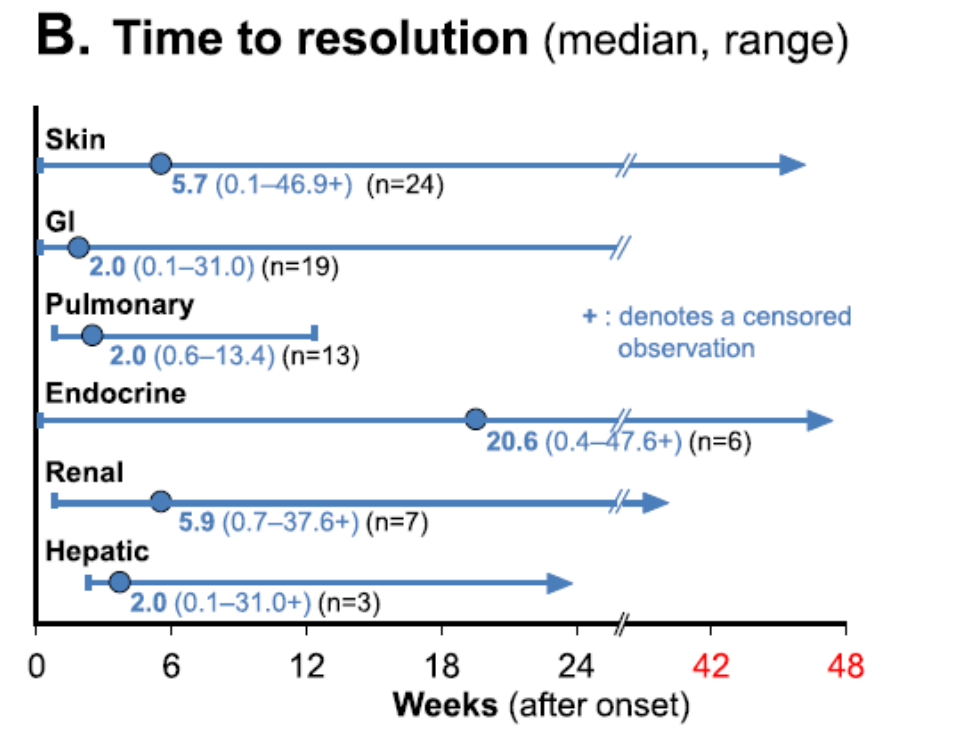


Timing of irAE on ipilimumab

Weber JS, et al. *J Clin Oncol* 2012;30:2691-7; Weber JS, et al. *J Clin Oncol* 2015;33:2092-9.

Onset and Resolution





irAEs and Clinical Outcomes

Cutaneous irAEs associated with improved outcomes in melanoma

- Moffitt Cancer Center study of 148 patients treated with nivolumab plus peptide vaccine or nivolumab alone
  - Statistically significant OS benefit with rash (p = .0001; HR, 0.423)
  - Statistically significant OS benefit with vitiligo (p = .012; HR, 0.184)
    - Rash and vitiligo correlated with OS differences in metastatic disease (p = .0004 and p = .028, respectively)
  - No significant survival differences seen with endocrinopathies, colitis, or pneumonitis in this study

Table 3. Effect of irAE development on survival, using time-dependent Cox regression analyses

	Univariate				Multivariate			
	HR	**LB**	**UB**	***P***	**HR**	**LB**	**UB**	***P***
Diarrhea/colitis	0.616	0.343	1.108	0.106	0.632	0.348	1.149	0.132
Hyperthyroidism	2.439	0.682	8.729	0.17	1.604	0.42	6.118	0.489
Hypothyroidism	0.37	0.104	1.325	0.127	0.36	0.1	1.291	0.117
Mucositis	0.09	0.005	1.49	0.093	0.087	0.005	1.448	0.089
Myalgias	0.313	0.019	5.192	0.418	0.377	0.022	6.477	0.502
Pneumonitis	0.346	0.021	5.729	0.459	0.371	0.022	6.313	0.493
Rash	**0.427**	0.246	0.74	**0.002**	**0.423**	0.243	0.735	**0.002**
Vitiligo	**0.178**	0.035	0.912	**0.038**	**0.184**	0.036	0.94	**0.042**

OS = overall survival; HR = hazard ratio.

irAEs and Clinical Outcomes (cont.)

Hypophysitis may be associated with improved outcomes

- Massachusetts General Hospital studied 154 patients treated with ipilimumab
  - Median survival in patients with ipilimumab-induced hypophysitis was 19.4 vs. 8.8 months (p = .05)

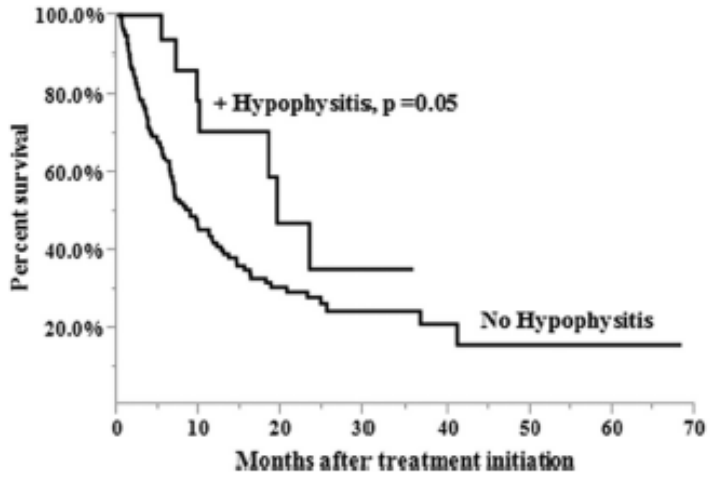


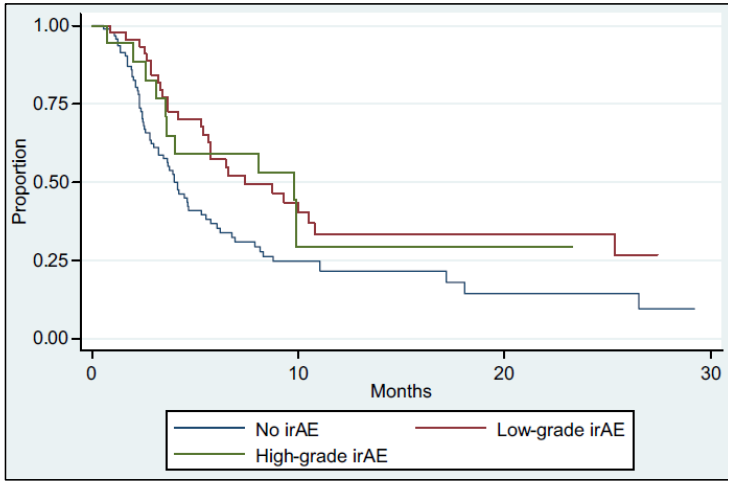
Figure 3. Kaplan-Meier plots for survival in metastatic melanoma patients, with and without hypophysitis, after the initiation of Ipi.

Faje AT, et al. *J Clin Endocrinol Metab* 2014;99:4078-85.

irAEs and Clinical Outcomes (cont.)

Positive association between development of irAE and clinical outcomes in non-melanoma patients

- Retrospective review of 160 non-melanoma patients at Fox Chase treated with immune checkpoint inhibitor
- Low-grade irAE had higher overall response rate and longer time to next therapy or death (TTNTD)
- No association between irAE and overall survival
- irAE requiring steroid treatment marginally associated with increased TTNTD

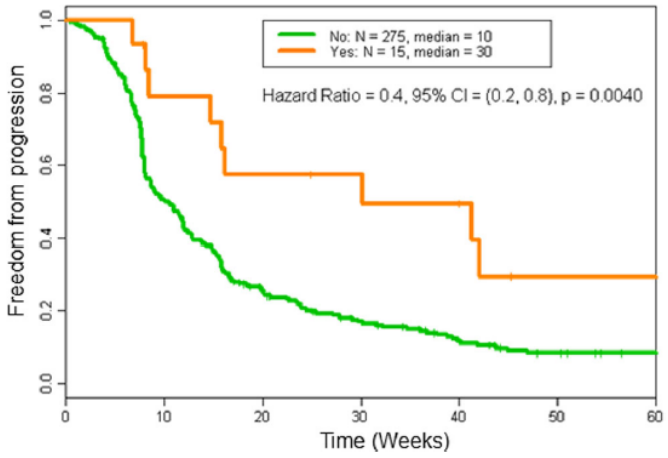


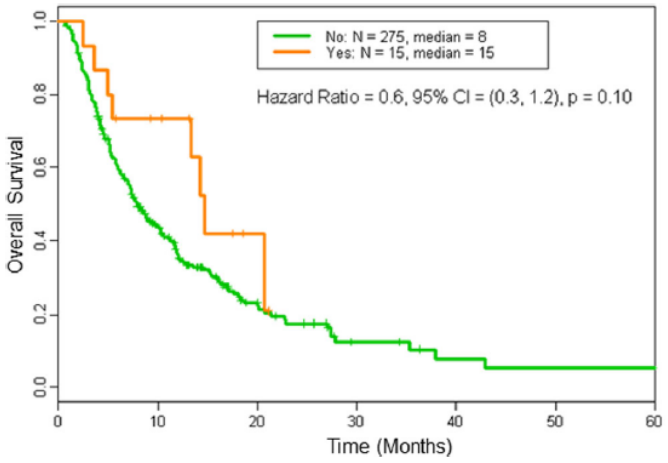
TTNTD: Statistically significant relationship between irAE and TTNTD

Judd, J., et al. (2017). Immune-related adverse events as a biomarker in non-melanoma patients treated with programmed cell death 1 inhibitors. *The Oncologist*, 22, 1-6.

irAEs and Clinical Outcomes (cont.)

- Retrospective study at MD Anderson evaluating 290 patients with advanced cancer treated on immunotherapy-based clinical trial
  - 34% experienced any grade irAE and 15% with ≥ G3 irE
  - Patients with ≥ G3 irAE had improved overall response rate (25% vs. 6%) and longer median time to progression (30 weeks vs. 10 weeks)

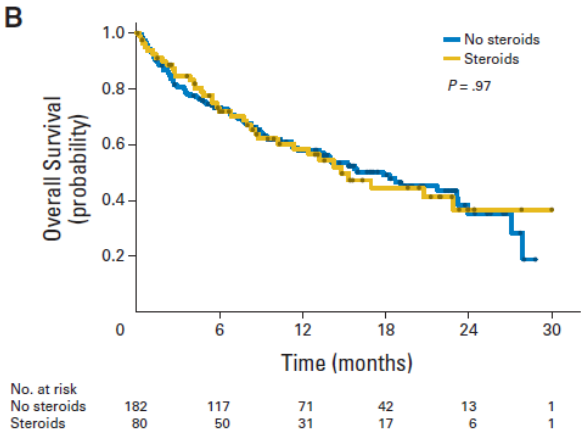


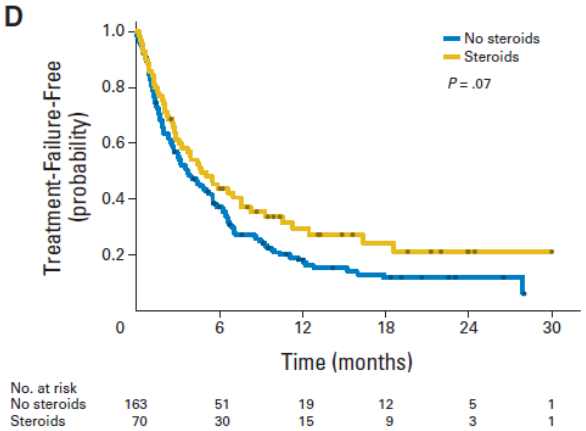


Fujii, T. et al. (2017) . Incidence of immune-related adverse events and its association with treatment outcomes: the MD Anderson Cancer Center experience. *Invest New Drugs*, doi: 10.1007/s10637-017-0534-0

Steroids: Do They Impact Efficacy?

- Retrospective study of 298 patients with melanoma treated with ipilimumab
- irAE, any grade: 254 (85%)
- Steroid therapy required: 103 (35%)
- Time to treatment failure, OS: the same in both groups

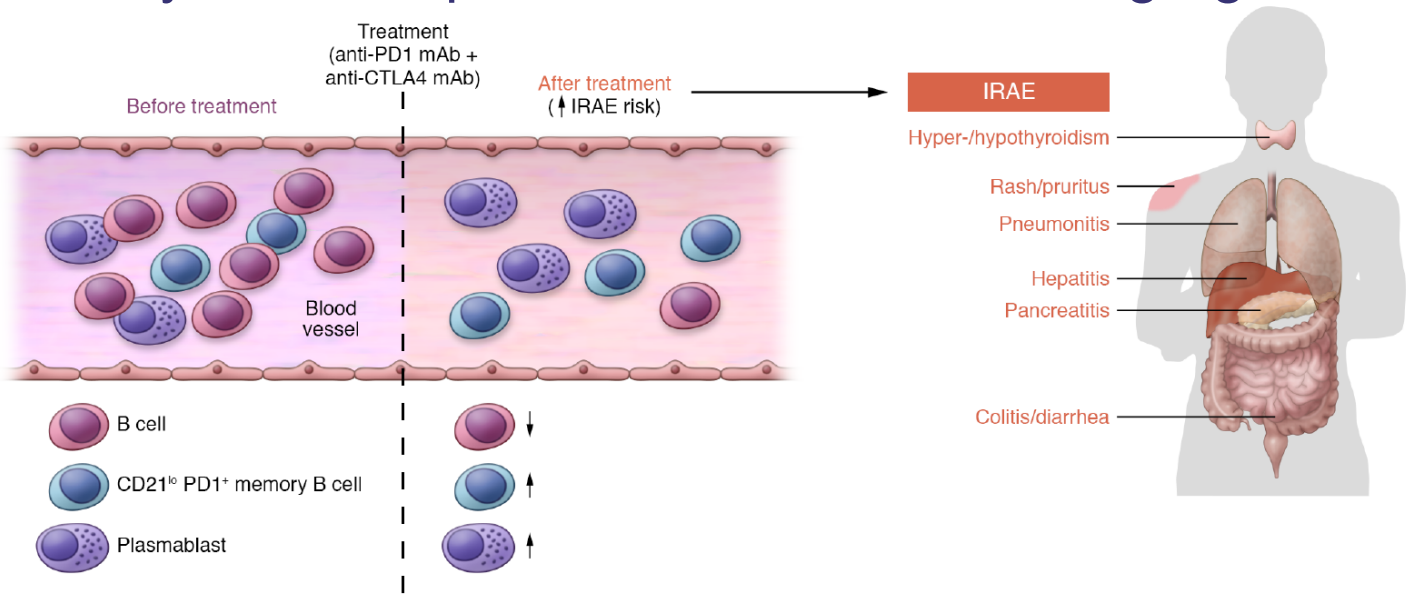




Horvat TZ, et al. *J Clin Oncol* 2015;33:3193-8.

Biomarkers and irAEs

- Goal to define risk factors for development of irAE
- Hypothesis that early therapy-induced changes in circulating B cells may serve as predictive biomarker for high-grade irAE



Liudahl, S.M. & Coussens, L.M. (2018). B cells as biomarkers: predicting immune checkpoint therapy adverse events. *Journal of Clinical Investigation*, 128(2), 577-579

Safety of Re-treatment After a Major Adverse Event

- Study of melanoma patients who experienced severe toxicity on ipilimumab who went on to receive anti–PD-1
  - Rare to experience recurrence of same irAE
  - New irAE occurred frequently and many were high grade (21% grade 3 or 4)
  - Data suggests that patients with prior ipilimumab toxicity are at increased risk of anti–PD-1 related toxicities, but such toxicities are generally manageable

Table 4. Toxicity of anti-PD-1 antibodies in patients with major ipilimumab toxicity

	Number (%) ($N = 67$)	Details
Ipi irAE recurrence on PD1		
No	65 (97%)	
Yes	2 (3%)	Arthritis, colitis
Other irAEs with PD1		
No	44 (66%)	
Yes	23 (34%)	
G1-2	9 (13%)	Colitis 3, hepatitis 1, arthritis 1, rash 2, neuropathy 1, hypothyroidism 1
G3	12 (18%)	Colitis 5, hepatitis 1, arthritis 1, myasthenia 1, pneumonitis 3, DKA 1
G4	2 (3%)	Hepatitis 1, pneumonitis 1
Immunosuppression required for irAE		
Symptomatic management	6 (9%)	
Oral steroids	10 (15%)	
SSA	1 (1%)	
IV steroids	4 (6%)	
Steroids and SSA	2 (3%)	
PD1 dosing with irAE		
Continue	9 (13%)	
Interrupt	6 (9%)	
Permanently discontinue	8 (12%)	Pneumonitis 4, hepatitis 2, colitis 1, myesthenia gravis 1

PD1, anti-PD-1 antobody; ipi, ipilimumab; DKA, diabetic ketoacidosis; SSA, steroid-sparing agent.

Menzies, A.M. et al. (2017). Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Annals of Oncology*, 28, 368-376.

Principles of IO Rechallenge

- Exercise caution when considering resumption of IO after significant irAE
- Permanent discontinuation of a given class of IO is warranted in setting of severe irAE induced by that class of IO and may be warranted in setting of moderate irAE
- With some exceptions, resumption of IO following grade 2 irAEs can be considered upon resolution to ≤ grade 1

Is it Necessary to Restart Treatment After Resolution of an Adverse Event?

- Additional prospective studies needed to confirm that extent of benefit is not affected by a shorter duration of immunotherapy.
  - In a study involving patients with advanced melanoma who were treated with a combination of nivolumab and ipilimumab, those who discontinued treatment because of toxicity during the first 4 months had rates of progression-free and overall survival that were similar to the rates for patients who continued therapy longer.
  - In a series of patients with NSCLC who had favorable response to immune checkpoint inhibitor treatment and then had an irAE that resulted in treatment discontinuation or delay, rates of progression-free and overall survival among patients who restarted were similar to those who permanently discontinued treatment.

Postow et al. (2018). Immune-related adverse events associated with immune checkpoint blockade. *NEJM*, 378(2).

Potentially At-Risk Populations

- **Autoimmunity**
  - Studies done in both PD-1 and CTLA-4 showing tolerable AE profile and similar efficacy
  - Treatment with either anti–PD-1 or anti–CTLA-4 is likely feasible, especially in metastatic setting
  - Recommend great caution using combined checkpoint inhibition
- **Transplant**
  - Preclinical data suggest that PD-1/PD-L1 axis may be particularly critical for maintaining organ tolerance
  - Anti–CTLA-4 may be safer in this setting
  - All checkpoint inhibitors carry significant risk of graft rejection and should be used with extreme caution
- **Chronic viral infections**
  - Very little experience; studied in HCC with Hep B or Hep C with manageable safety profile
  - Ongoing trial evaluating pembrolizumab in patients with HIV and advanced cancer
  - HIV and hepatitis C are likely not contraindications for anti–PD-1 therapy

Johnson, D.B. et al. (2017). Immune checkpoint inhibitors in challenging populations. *Cancer*, 123, 1904-1911.

Unintended Effects of Immunosuppression

- Use of glucocorticoids can cause hyperglycemia, fluid retention, anxiety
  - Also iatrogenic adrenal insufficiency if tapered too quickly
- Long-term glucocorticoid therapy can lead to cushingoid features, osteoporosis, glaucoma, opportunistic infections, and severe proximal muscle weakness
- Immunosuppression may put patients at risk for opportunistic infections such as Aspergillus fumigatus pneumonia, cytomegalovirus hepatitis, and pneumocystis pneumonia
  - Retrospective study of 790 melanoma patients treated with checkpoint blockade found the rate of serious infections was 13.5% in the subgroup of patients who received wither glucocorticoids or infliximab for irAE

Postow et al. (2018). Immune-related adverse events associated with immune checkpoint blockade. *NEJM*, 378(2).

Principles of Routine Monitoring on IO

Baseline Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/ Symptoms
Clinical: • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency)	Clinical exam at each visit with AE symptom assessment	Follow-up testing based on findings, symptoms
Imaging: • CT imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General bloodwork: • CBC with differential • Comprehensive metabolic panel • Infectious disease screening as indicated	Repeat every 2–3 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated.
Thyroid • Thyroid-stimulating hormone (TSH), free thyroxine (T4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 if abnormal thyroid function suspected. TPO antibodies if TSH is high, TRAbs if TSH is low.
Adrenal/Pituitary • Adrenal: Morning adrenocorticotropic hormone (ACTH) and cortisol • Pituitary: TSH, free T4, and total T3	Every 2–3 weeks during immunotherapy, then follow-up every 6–12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone
Pulmonary • Oxygen saturation (resting and with ambulation) • Pulmonary function tests (PFTs)	Repeat oxygen saturation tests based on symptoms	Chest CT to evaluate for pneumonitis, biopsy if needed to exclude other causes
Cardiovascular • ECG and total CK • Cardiac biomarkers (ie, troponin I or T) if risk factors present	Consider periodic testing for those with abnormal baseline or symptoms	Brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT pro-BNP)
Pancreatic • Baseline amylase/lipase	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal imaging for suspected pancreatitis
Musculoskeletal • Joint examination/functional assessment as needed for patients with pre–existing disease	No routine monitoring needed if asymptomatic	N/A

Conclusions

- We are working towards a better understanding of the mechanism of immune related adverse events
- irAEs generally occur within the first weeks to months of therapy but can happen any time
- irAEs should be managed with the assistance of existing guidelines and in the setting of multidisciplinary collaboration
- It is possible to safely re-treat patients who have experienced an irAE, although it may not be necessary
- Previously excluded treatment populations (existing autoimmune disorders, history of transplant, viral infections, etc) can likely be treated safely with checkpoint inhibitors but further research is ongoing

Audience Response Question

Which of the following is true regarding immune-related adverse events?

A) Endocrine-related adverse events are usually the first to appear
B) Dermatologic-related adverse events are associated with a better response in patients with lung cancer
C) Patients with melanoma are more likely to develop pneumonitis than patients with other cancers
D) The incidence of specific adverse events varies based on the underlying cancer
E) Unsure

Audience Response Question

Your patient with melanoma receiving treatment with anti–PD-1 therapy develops a grade 2 dermatitis not responsive to topical therapy. You educate the patient that:

A) We will need to hold immunotherapy and treat the dermatitis with oral steroid. Oral steroid may decrease the efficacy of anti–PD-1 therapy.

B) We will need to hold immunotherapy and treat the dermatitis with oral steroid, but that the efficacy of immunotherapy is unaffected.

C) We will continue immunotherapy and treat the dermatitis with oral steroid. Oral steroid may decrease the efficacy of anti–PD-1 therapy

D) We will continue immunotherapy and treat the dermatitis with oral steroid, but that the efficacy of immunotherapy is unaffected

E) Unsure