Managing Side Effects of Cancer Patients Treated With Immunotherapy

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Learning Objectives

1. Identify patient education pearls regarding symptoms that warrant an immediate call to an oncologist or oncology advanced practitioner
2. Develop triage points to assess those side effects from immunotherapy that warrant immediate medical attention
3. Differentiate between early and late adverse effects associated with immunotherapeutic agents
4. Recognize the differences between immunotherapeutic agents and chemotherapeutic agents: mechanisms of action, adverse effects, and toxicity management
5. Assess the safety of using immunotherapeutic agents to treat cancer in patients with autoimmune disease
6. Describe the concept of “pseudo-progression” associated with immunotherapeutic agents and identify ways to differentiate this occurrence from real disease progression

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- Ms. Hoffner has served on an advisory board for Eli Lilly and Company.
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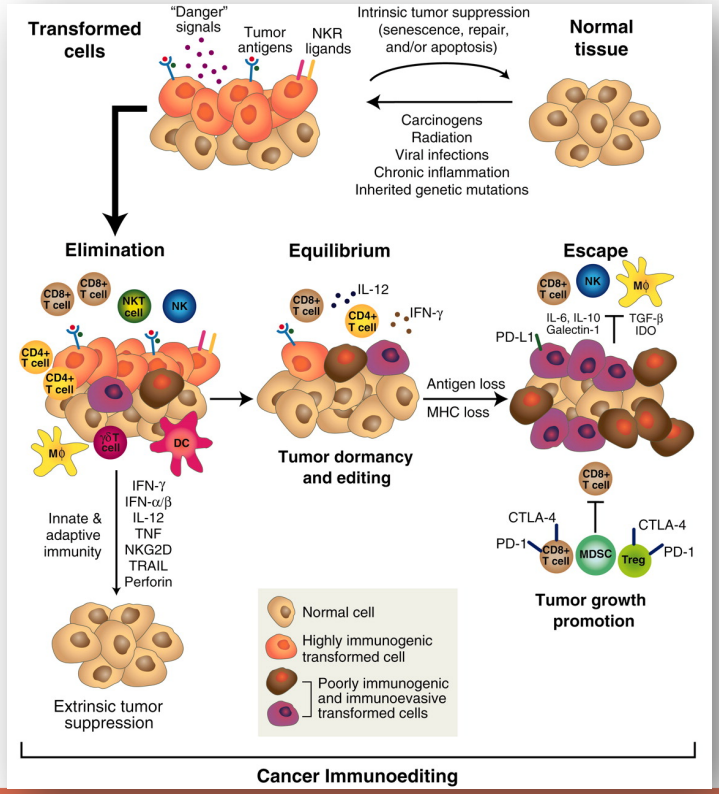
Immune-Related Adverse Events: Pathophysiology and General Approach

The Cancer Immunoediting Hypothesis

Elimination Phase
Tumor cells are immunogenic as they express new antigens recognized by the immune system. Innate and adaptive immunity work together to destroy developing tumors long before they become clinically apparent. If this phase is successful, the patient remains cancer-free.

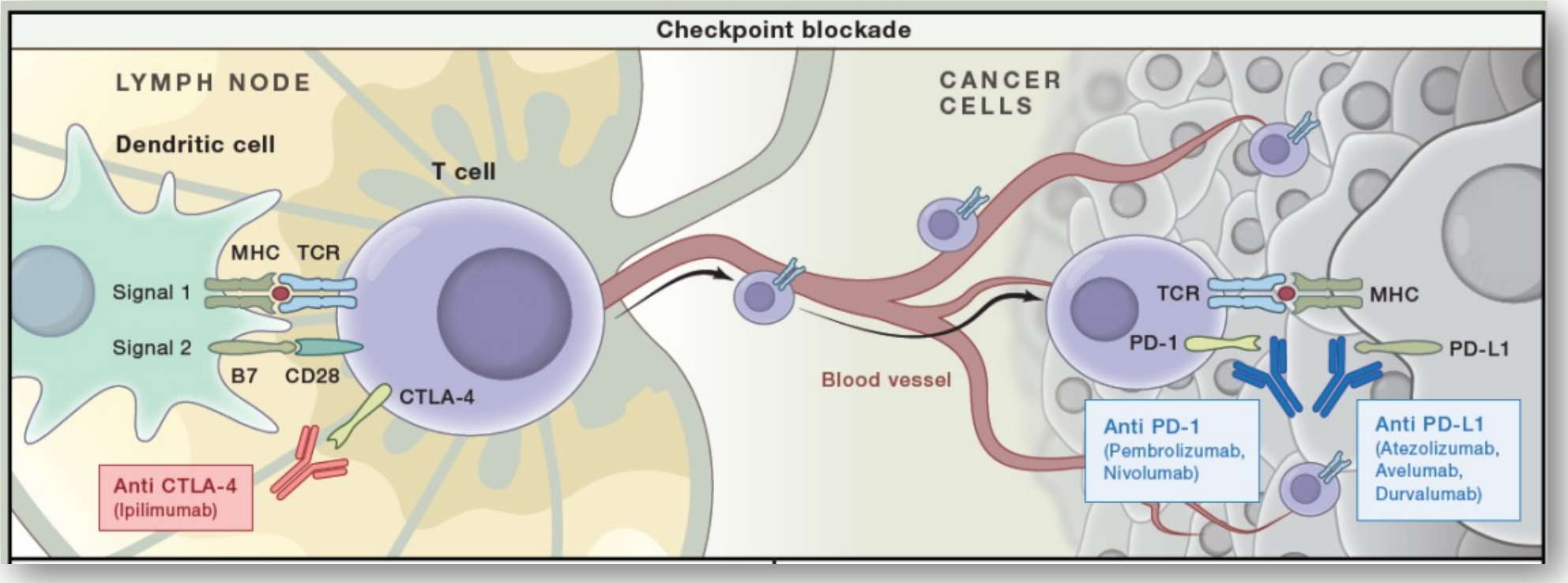


Equilibrium Phase
If a tumor cell escapes elimination, it can enter equilibrium phase where the immune system limits tumor growth. Constant selection pressure from the immune system allows tumor variants to emerge that can escape immune detection.

Escape Phase
The immune system no longer recognizes/suppresses tumor growth and clinically apparent cancer occurs.

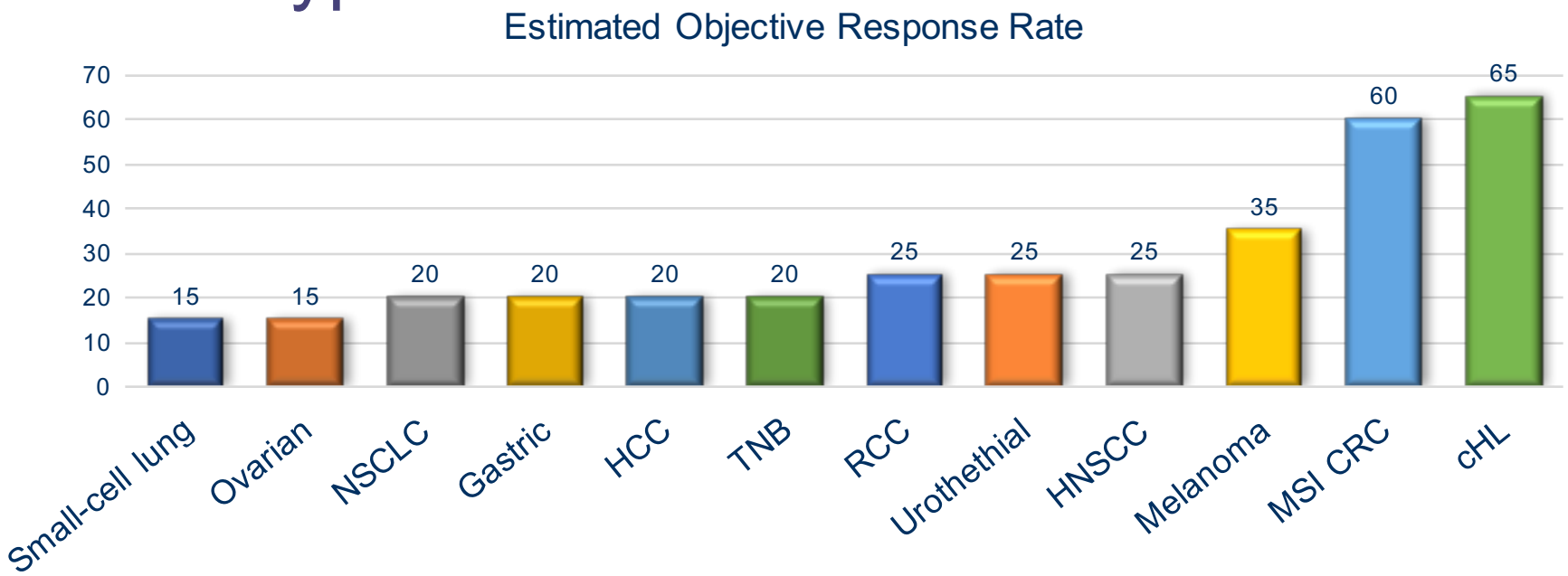
Schreiber RD, et al. *Science* 2011;331:1565-70.

Immune Checkpoint Inhibitors Counteract Peripheral T-cell Tolerance and Release the Brakes on the Immune System



Abril-Rodriguez G, et al. *Cancer Cell* 2017;31(6):848-848.e1.

Checkpoint Inhibitors Effective for Many Tumor Types



cHL = classical Hodgkin lymphoma; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; MSI CRC = microsatellite instability in colorectal cancer; NSCLC = non–small cell lung cancer; RCC = renal cell carcinoma; TNB = triple-negative breast cancer.

Champiat S, et al. *Ann Oncol* 2016;27:559-74; Chiou VL, et al. *J Clin Oncol* 2015;33:3541-3.

FDA Approvals (as of 10/22/2017)

Indication	Anti-CTLA-4	Anti-PD-1		Anti-PD-L1		
	Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Avelumab	Durvalumab
Melanoma, adjuvant						
Melanoma, metastatic, 1st line						
mNSCLC, 1st line			Single agent or combination with premetrexed/carboplatin			
mNSCLC, 2nd line						
Hodgkin Lymphoma, relapsed, 4th line						
HNSCC, metastatic, 2nd line						
Microsatellite Instability-High Cancer, metastatic, 2nd line						
Renal cell, advanced, 2nd line						
Bladder, metastatic, 2nd line						
Merkel cell, metastatic, 1st line						

FDA = US Food and Drug Administration; mNSCLC = metastatic non–small cell lung cancer.

Compiled from FDA approvals listed on company websites (AstraZeneca, Bristol-Myers Squibb, EMD, Merck, Genentech).

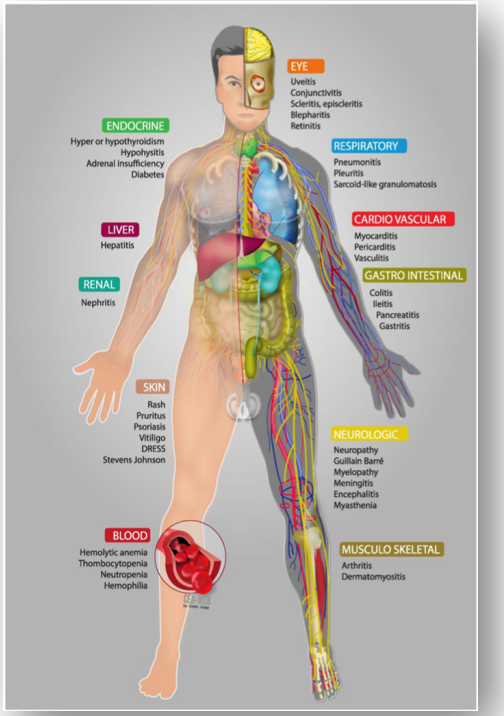
Releasing the Brakes on T Cells May Cause Immune-Related Adverse Events in Any Tissue

Common (> 10%)

- Dermatitis, pruritus
- Fevers, chills, fatigue
- Diarrhea/colitis

Infrequent (5%–10%)

- Hepatitis/liver enzyme abnormalities
- Endocrinopathies: hypophysitis, thyroiditis, adrenal insufficiency

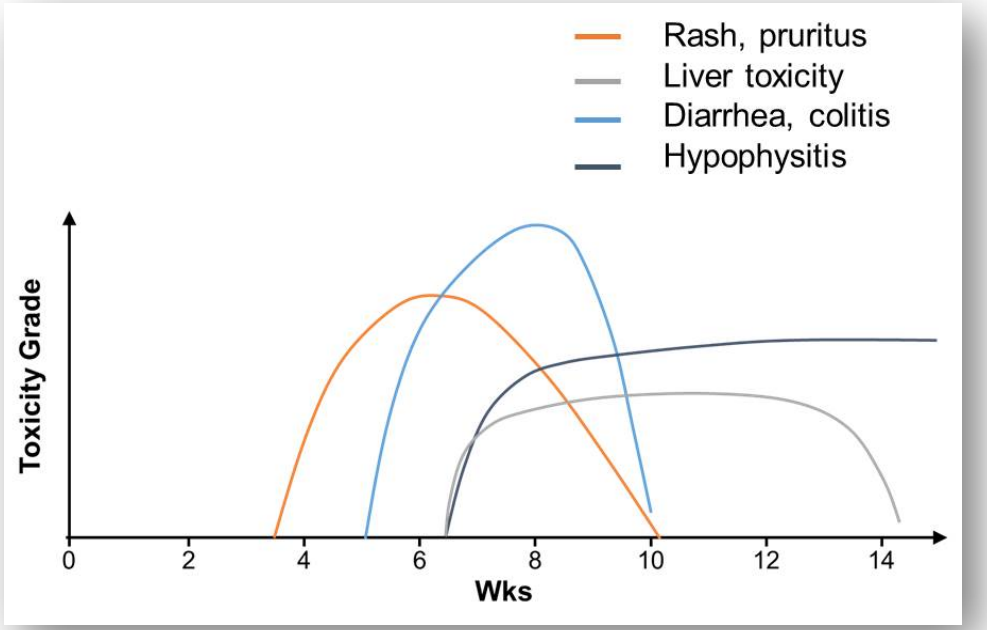


Rare (< 5%)

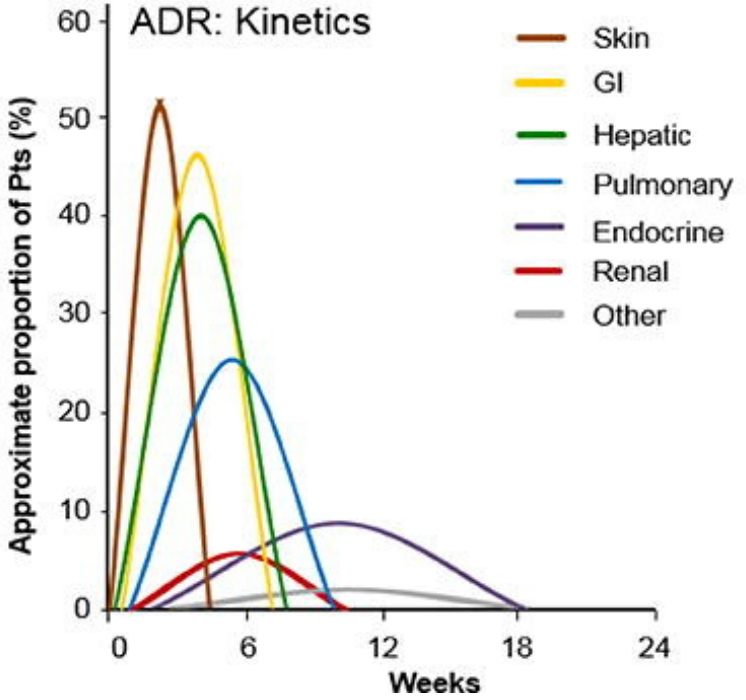
- Encephalitis
- Episcleritis/uveitis
- Myocarditis
- Pneumonitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barré, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia
- Toxic epidermal necrolysis, Stevens-Johnson syndrome

Champiat S, et al. *Ann Oncol* 2016;27:559-74.

Timing of Immune-Related Adverse Events (irAEs)



Single Agent[1]



Combination Therapy[2]

1. Weber JS, et al. *J Clin Oncol* 2012;30:2691-7 2. Hassel, J. C., et al. Cancer Treatment Reviews, 2017, 57, 36-59

Recommended Tests

Baseline	Prior to Each Treatment
• Complete blood count • Complete metabolic panel with LFTs • TSH, fT4 • CXR, ECG • UA (for protein) • Consider: • CRP, 8 am cortisol and ACTH	• Complete blood count • Complete metabolic panel with LFTs • TSH, fT4 every 1–3 months

ACTH = adrenocorticotropic hormone; CRP = C-reactive protein; CXR = chest x-ray; ECG = electrocardiogram; fT4 = free thyroxine; LFTs = liver function tests; TSH = thyroid-stimulating hormone; UA = urinalysis.

Champiat S, et al. *Ann Oncol* 2016;27:559-74; Weber JS, et al. *J Clin Oncol* 2015;33:2092-9. Hassel, J. C., et al. Cancer Treatment Reviews, 2017, 57, 36-59

Management Approach to irAEs

CTCAE Grade	Ambulatory vs. inpatient care	Corticosteroids	Other immunosuppressives	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids for skin toxicity or Systemic steroids oral 0.5–1 mg/kg/day	Not recommended	Suspend temporarily (not necessary to suspend therapy for skin or endocrine disorders)
3	Hospitalization	Systemic steroids oral or IV 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	Consider for patients with unresolved symptoms after 3–5 days of steroids; organ specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization; consider intensive care unit	Systemic steroids IV methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	Consider for patients with unresolved symptoms after 3–5 days of steroids; organ specialist referral advised	Discontinue permanently

IV = intravenously.

Champiat S, et al. *Ann Oncol* 2016;27:559-74; Haanen, J. B. A. G., et al. Annals of Oncology. 2017, 28(suppl_4), iv119-iv142. Weber JS, et al. *J Clin Oncol* 2015;33:2092-9.

Management Approach for Steroid Refractory

Figure 3. Treatment of Severe and Steroid-Refractory Immune-Related Adverse Effects (irAEs)

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 CF, et al. *JAMA Oncol* 2016;2(10):1346-53.

When Would You Consider Restarting Immunotherapy?

- If the side effect resolves
- If the steroid dose is reduced to ≤ 10 mg/day prednisone or equivalent
- In the absence of other immunosuppressive drugs
- Endocrinopathies controlled by hormone replacement therapy generally do not require the termination of immunotherapy

Management of Side Effects of Steroids

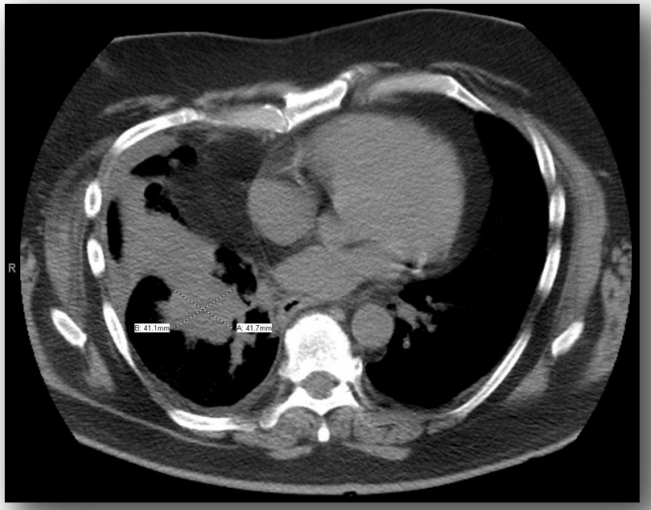
- H2 blocker for GI prophylaxis
  - Famotidine, ranitidine, etc.
- Clotrimazole troches for thrush prevention
- PCP prophylaxis for prednisone ≥ 20 mg/d for more than 4 weeks
  - Sulfamethoxazole/trimethoprim SS 1 tab PO daily

PCP = pneumocystis jirovecii pneumonia; PO = by mouth.

Case Study: JL

Case Study: JL

- JL is a 65-year-old male, nonsmoker
- Diagnosed 6/21/2017 with stage IV adenocarcinoma of lung involving right lung, right hilar, mediastinal lymph nodes, right pleural nodularity with malignant right pleural effusion
- Molecular status
  - *ALK* rearrangement negative, *ROS1* negative, *MET* amplification negative, *RET* rearrangement negative, NGS showed no *EGFR, KRAS, BRAF*, or *HER2*/neu; PD-L1 negative



Right Infrahilar Mass

NGS = next-generation sequencing.

Case Study: JL

- JL's past medical history
  - Arthritis
  - Gastroesophageal reflux disease
  - Hyperlipidemia
  - Hypertension
  - Hypothyroidism
- Meds: levothyroxine, losartan, metoprolol

- JL is started on pembrolizumab, carboplatin and pemetrexed
  - C1D1: 7/3/17
  - C2D1: 7/24/17
  - C3D1: 8/14/17
  - C4D1: 9/4/17
- Tolerated first 4 cycles well without irAE
- Scans after C4 show 35% decrease in disease burden

Case Study: JL

- 9/25/17: Presents for C5 (pembrolizumab only) complaining of increased fatigue, urinary hesitancy and dyspnea on exertion
- Pertinent laboratory findings:

	9/4/17	9/25/17
Hgb (14.3–18.1 g/dL)	9.1	7.8
MCV (80–100 fL)	85	82
Sodium (133–145 mmol/L)	135	130
BUN (7–25 mg/dL)	14	16
Creatinine (0.7–1.3 mg/dL)	1.1	4.0
TSH (0.34–5.60 mIU/L)	NA	1.95

BUN = blood urea nitrogen; Hgb = hemoglobin; MCV = mean corpuscular volume.

Case Study JL: Differential Diagnoses

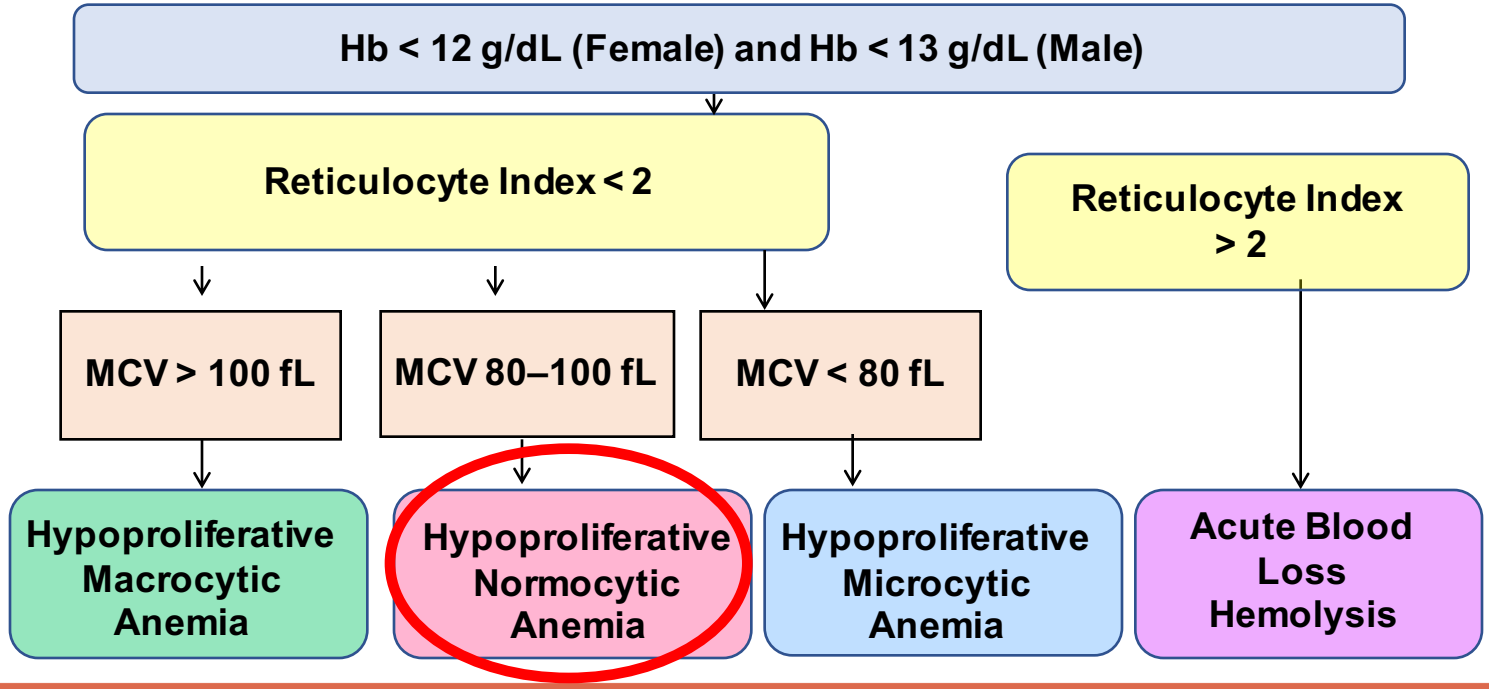
- Grade 3 anemia
  - Anemia of chronic disease
    - Secondary to lung cancer
    - Secondary to thyroid dysfunction
    - Secondary to kidney dysfunction
  - Iron deficiency anemia
    - Secondary to blood loss
    - Secondary to insufficient dietary iron
- Grade 3 creatinine increased
  - Nephritis
  - Nephrotoxicity from chemotherapy
  - Dehydration
  - Other drug injury
  - Hypertension

Case Study JL: Anemia

Add-on labs to include reticulocyte count and iron studies:

Reticulocyte count (0.5%–2.5%)	0.90%
Hgb (14.3–18.1 g/dL)	7.8
MCV (80–100 fL)	82
Iron serum (45–160 ug/dL)	30
Transferrin (203–362 mg/dL)	299
Ferritin (11–307 ng/mL)	150

Diagnostic Evaluation of Anemia Based on MCV and Reticulocyte Index



Camaschella C. *Hematology* 2015;2015:8-13.

Differential Diagnosis of Anemia

MICROCYTIC ANEMIA
- Iron deficiency
- Thalassemia
- Lead toxicity
- Sideroblastic anemia
- Anemia of chronic disease (late, uncommon)

NORMOCYTIC ANEMIA
- Anemia of chronic disease (CKD, malignancy, heart failure, endocrine dysfunction)
- Blood loss
- Iron deficiency anemia (early)
- Bone marrow disorders
- Bone marrow suppression (drugs, chemotherapy, radiation)
- Low levels of hormones
  - EPO deficiency (CKD)
  - Thyroid hormone (hypothyroidism)
  - Androgens (hypogonadism)

MACROCYTIC ANEMIA
- Folate or vitamin B_{12} deficiency
- Medications (AZT, hydrea, imatinib, sunitinib, methotrexate, 6MP, capecitabine, cladribine, cytarabine)
- Alcohol abuse
- Hypothyroidism
- Certain bone marrow disorders (MDS, leukemia, pure red cell aplasia)
- Increased reticulocytes (hemolytic anemia)

☐ Decreased RBC production
■ Increased RBC destruction or loss

6MP = mercaptopurine; AZT = azidothymidine; CKD = chronic kidney disease; EPO = erythropoietin; MDS = myelodysplastic syndrome; RBC = red blood cell.

Cascio MJ, et al. *Med Clin North Am* 2017;101:263-84.

Case Study JL: Anemia

- Hypoproliferative normocytic anemia
  - No sign of early iron deficiency on labs
  - Blood pressure is well controlled
  - Kidney disease is acute, not chronic
  - Thyroid function is well preserved with replacement
- Likely related to chemotherapy
  - 12.9% incidence of grade 3 anemia with carboplatin/pemetrexed[1]

1. Xu H, et al. *Clin Epidemiol* 2016;8:61-71.

Case Study JL: Creatinine Increased

- FENa > 1%
- Urine culture: negative

	Reference & Units	Result
Color urine	Yellow	Yellow
Appearance urine	Clear	Clear
Specific gravity urine	1.001–1.035	1.012
pH urine	5.0-8.0	6.0
Protein urine	Negative mg/dL	1+
Glucose urine	Negative mg/dL	50
Ketones urine	Negative mg/dL	80
Bilirubin urine	Negative	Negative
Blood urine	Negative	Small
Nitrite urine	Negative	Negative
Urobilinogen urine	< 2.0 EU/dL	< 2.0
Leukocyte esterase urine	Negative	Trace
White blood cells urine	0–5 /HPF	38
Red blood cells urine	0–3 /HPF	4
Squamous epithelial cells	Occasional/HPF	Occasional

FENa = fractional excretion of sodium;
HPF = high power field.

Nephritis

The most typical clinical presentation is a rise in creatinine with mild proteinuria and/or pyuria.

- Rare side effect estimated to occur in 2% of patients
- Incidence higher with combination therapy
- Median time to onset:
  - Ipilimumab: 2–3 months
  - PD-1/PD-L1 inhibitors: 3–10 months
- Majority of patients recover renal function with steroids
- Recovery of renal function takes weeks

Cortazar FB, et al. *Kidney Int* 2016;90:638-47; Haanen, J. B. A. G., et al. Annals of Oncology. 2017, 28(suppl_4), iv119-iv142. Hassel, J. C., et al. Cancer Treatment Reviews, 2017, 57, 36-59. Wanchoo R, et al. *Am J Nephrol* 2017;45(2):160–9.

Case Study JL: Conclusion

- Grade 3 anemia related to chemotherapy
  - Recovered in time off of chemo
- Grade 3 nephritis related to pembrolizumab
  - Treated with prednisone 1 mg/kg for a month, and serial Cr was measured 2x per week
  - Renal function recovered after 4 weeks, and the steroids were tapered over 8 weeks
  - Treated with sulfamethoxazole and trimethoprim for PCP prophylaxis, clotrimazole troches for thrush prevention and famotidine for gastritis prevention
  - Pembrolizumab discontinued
    - In the approval study, the most common adverse reaction resulting in discontinuation of pembrolizumab (≥ 2%) was acute kidney injury (3.4%)[1]

Cr = creatinine.

1. FDA Press Release, Pembrolizumab (Keytruda) 5-10-2017, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm558048.htm.

Case Study: HT

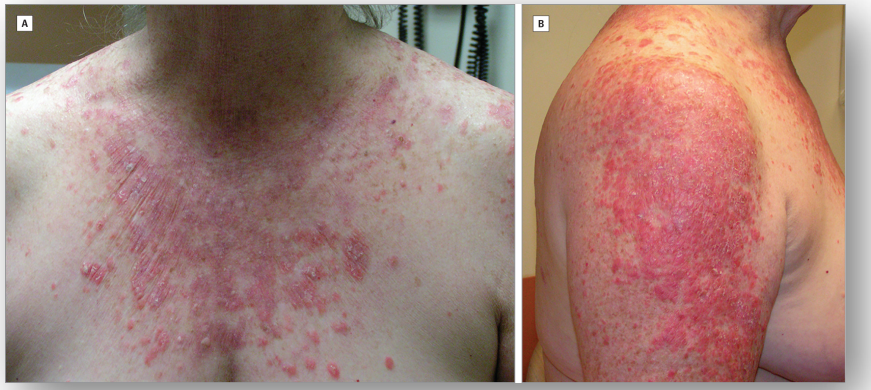
Case Study: HT

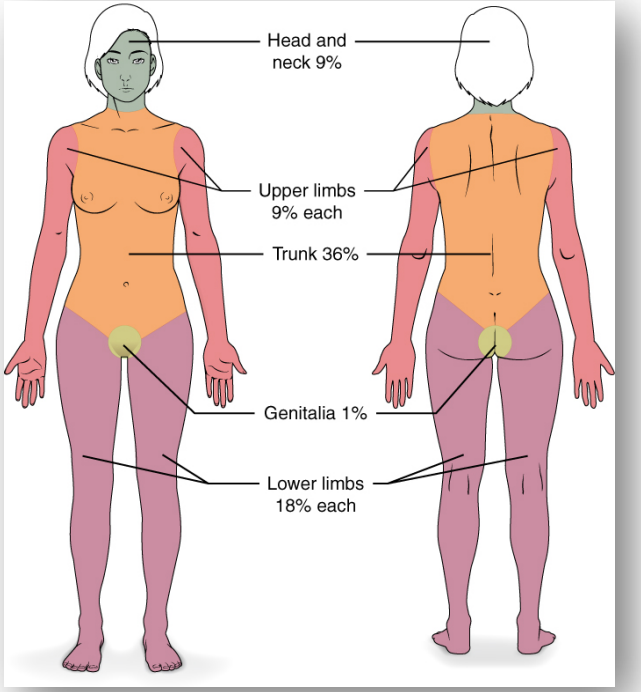
- 62-year-old female diagnosed 2016 with stage III colon cancer
- Underwent surgical resection and adjuvant FOLFOX
- 2017: developed single liver metastasis, MSI-high
- Liver metastasis resected followed by FOLFIRI plus bevacizumab and 10 months of maintenance bevacizumab plus 5-FU
- Progressive disease in liver and developed two small pulmonary lesions
- Started nivolumab 240 mg IV over 60 minutes every 2 weeks

FOLFIRI = 5-FU/leucovorin/irinotecan; FOLFOX = 5-FU/leucovorin/oxaliplatin.

Case Study: HT

- Week 5: called clinic to report pruritic rash
- Exam in clinic: maculopapular eruption on chest and upper arms
  - Grade 2 (10%–30% BSA)





BSA = body surface area.

Sanlorenzo M, et al. *JAMA Dermatology* 2015;151:1206-12.

Case Study: HT

Grade 2 dermatitis: 10%–30% BSA affected

- Treated with supportive care measures and prednisone 0.5 mg/kg/d
- Hydroxyzine for pruritus
- Delayed nivolumab until rash resolved 1 week later
- Prednisone tapered over 4 weeks
- Nivolumab (cycle 3) restarted week 8 when prednisone dose 10 mg/d
- Steroids discontinued week 9
- Week 12: presented for cycle 5 and CMP significant for the following labs:
  - ALT: 160 (normal 7–52 U/L)
  - AST: 143 (normal 12–39 U/L)
  - T bili: 1.5 (normal 0.1–1.3 mg/dL)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMP = comprehensive metabolic panel; T bili = total bilirubin.

Case Study: HT

- Grade 2 elevation ALT/AST and grade 1 elevation T bili
  - CT abd: stable liver metastases
  - Infectious hepatitis testing negative
- Diagnosis: autoimmune hepatitis
  - Held immunotherapy
  - Restarted prednisone 0.5 mg/kg and LFTs normalized in 3 days
  - Rechecked labs after 2 days of steroids:

	Week 12	After Steroid
ALT (7–52 U/L)	160	102
AST (12–39 U/L)	143	98
T Bili (0.1–1.3 mg/dL)	1.5	1.3

- Grade 1 elevation AST/ALT
  - Taper 10–20 mg per week based on LFT values

CT abd = computed tomography of the abdomen.

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

Case Study: HT

- Week 15: prednisone decreased to 10 mg/d so restarted immunotherapy
- Presented week 20 with fatigue, cold intolerance
  - TSH: 9 µIU/L (normal 0.3–3.0 µIU/mL)
  - free T4: 0.2 ng/dL (normal 0.7–1.8 ng/dL)
  - Antithyroglobulin and antithyroid peroxidase positive
- Diagnosis: hypothyroidism due to autoimmune thyroiditis
- Treatment
  - Hormone replacement: levothyroxine 1.6 µg/kg/d
  - Does not require corticosteroids
  - Advised patient that she will likely need lifelong thyroid replacement therapy
  - OK to continue immunotherapy

Diagnosis	TSH	Free T4
Primary hypothyroidism	High	Low
Subclinical hypothyroidism	High	Normal
Secondary hypothyroidism due to abnormal pituitary function	Normal (some cases may be low or high)	Low (some cases may be low-normal)

Ross DS, Diagnosis of Hyperthyroidism, https://www.uptodate.com/contents/diagnosis-of-hyperthyroidism;
Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207.

Case Study HT: Conclusion

- Grade 2 dermatitis
  - Developed at week 5, treated with prednisone 0.5 mg/kg/day
- Grade 2 hepatitis
  - Developed at week 12, treated with prednisone 0.5 mg/kg/day
- Grade 2 hypothyroidism
  - Developed at week 20, treated with levothyroxine 1.6 µg/kg/d
- Due to early recognition and appropriate management, patient was able to stay on therapy despite multiple irAEs

Other irAEs

Autoimmune Hyperthyroidism

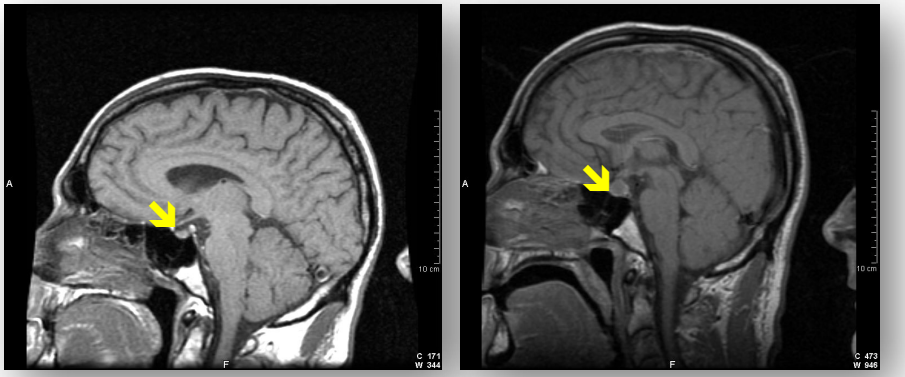
- Generally asymptomatic
- If symptomatic: beta-blocker
- Consider delaying immunotherapy
- Radioactive iodine uptake generally inaccurate
- Antithyroglobulin and antithyroid peroxidase generally positive
- Generally self-limiting (within ~4 weeks)
- Monitor for subsequent hypothyroidism

Diagnosis	TSH	Free T4
Primary hyperthyroidism	Low	High
Subclinical hyperthyroidism	Low	Normal

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

Hypophysitis: Inflammation of the Pituitary Gland

- Results in deficiency of all or some of the pituitary hormones
- 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)
- Workup
  - Evaluation of pituitary gland hormones (ACTH, TSH, FSH, LH, prolactin, cortisol)
  - MRI brain with contrast (pituitary cuts)
- Treatment
  - High-dose steroid for critical illness
  - Low-dose glucocorticoid to alleviate headache/fatigue
  - Replace pituitary hormone deficiencies (start with adrenal insufficiency)



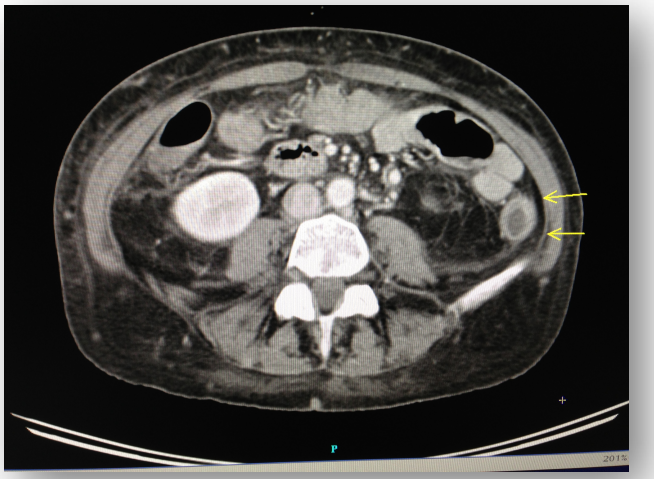
Pre-ipilimumab **Post-ipilimumab**

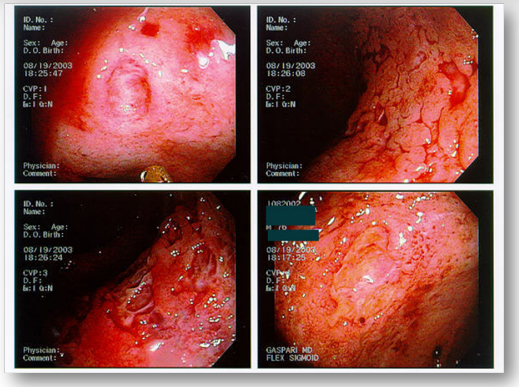
ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; LH= luteinizing hormone; MRI = magnetic resonance imaging.

Michot JM, et al. *Eur J Cancer* 2016;54:139-48; Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207;
Images courtesy Brianna Hoffner, University of Colorado.

Diarrhea and/or Colitis

- Symptoms
  - Abdominal cramping, pain
  - Anorexia, dyspepsia
  - Diarrhea, blood or mucous in stool
  - Possible to have colitis without diarrhea
- Workup
  - Stool for C. diff, ova and parasite, blood
  - CT abdomen/pelvis with IV contrast
  - Colonoscopy with biopsy
- Prevention with budesonide (oral); randomized phase II trial no benefit shown[1] but it may have a role for treatment of grade 2 irAE[2]
- Diarrhea/colitis with one checkpoint inhibitor does not prohibit use of another[3]





C. diff = clostridium difficile.

1. Weber J, et al. *Clin Cancer Res* 2009;15:5591-8; 2. Haanen, J. B. A. G, et al. Annals of Oncology 2017, 28(suppl_4), iv119-iv142. 3. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53; Images courtesy Brianna Hoffner, University of Colorado.

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 (pericarditis)
- Late diagnosis may lead to chronic, irreversible lung disease[2]

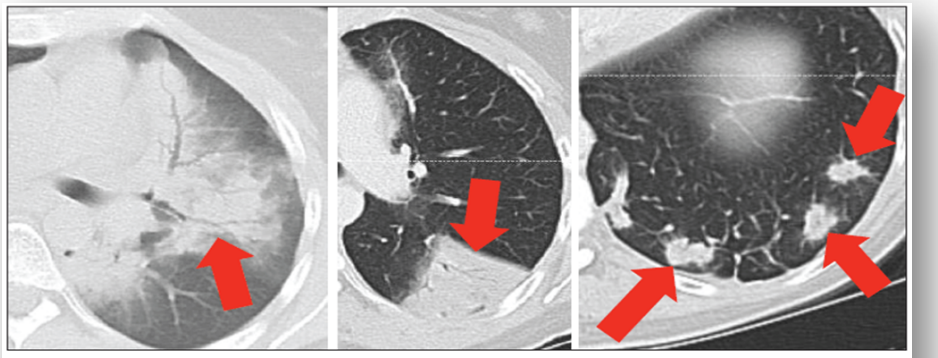


Figure 3: Different Radiographic Patterns of Checkpoint Blockade–Associated Pneumonitis Seen on CT Scanning in a Single Patient Treated With Ipilimumab and Nivolumab—Pneumonitis secondary to ipilimumab is shown in the left-hand panel, and pneumonitis secondary to nivolumab is shown in the center and right-hand panels. Red arrows indicate areas of radiologic abnormality.

1. Michot JM, et al. *Eur J Cancer* 2016;54:139-48; 2. Eigentler TK, et al. *Cancer Treat Rev* 2016;45:7-18.
3. Image Credit: Teply BA, et al. *Oncology (Williston Park)* 2014;28 Suppl 3:30-8.

Other irAEs

Type 1 Diabetes Mellitus

- Rare occurrence with PD-1 (< 0.1%)
- Patients generally present in DKA[1]
- Workup: GAD65 antibodies
- Treatment with insulin therapy

Oral Mucosa[2,3]

- Mucositis, gingivitis, and sicca (Sjogren) syndrome
- Workup: ANA and SSA/SSB screen
- Management
  - Oral corticosteroid rinses
  - Pilocarpine chlorhydrate
  - Viscous lidocaine
  - Good oral hygiene

ANA = antinuclear antibody; DKA = diabetic ketoacidosis; GAD65 = glutamic acid decarboxylase 65.

1. Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207 2. Michot JM, et al. *Eur J Cancer* 2016;54:139-48;
3. Friedman CF, et al. *JAMA Oncology* 2016;2:1346-53.

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]

Neurologic[1]

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

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

Other irAEs

Polyarthritis/arthralgia[1]

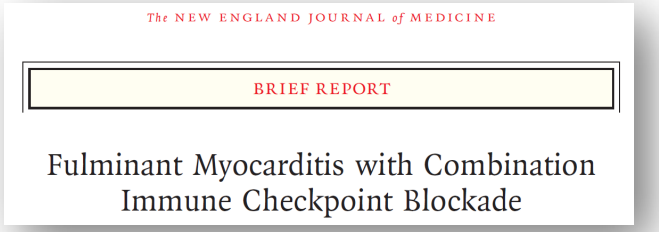
- Seen in approximately 5% of patients
- Reported cases erythematous lupus or polymyalgia rheumatic
- ANA and anti-cyclic citrullinated peptide to detect autoimmune condition
- Low-dose oral steroid to control joint manifestations

Hematologic toxicity

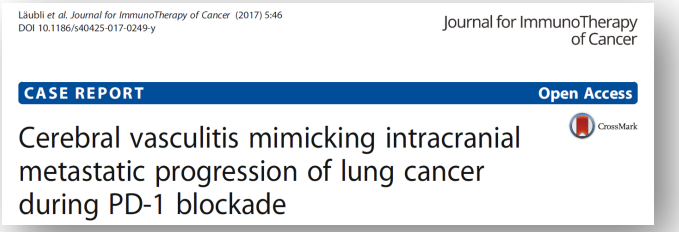
- Anemia described in < 5% CTLA-4 and < 10% PD-1[2]
- Red cell aplasia, autoimmune neutropenia, pancytopenia, acquired hemophilia A also reported[1]
- Workup to include peripheral smear, reticulocyte count, Coombs test, hemolysis assays, and bone marrow biopsy[1]

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

Emerging Reports of irAEs



- Two patients with melanoma developed fatal myocarditis after ipilimumab/nivolumab
- Myocarditis with robust presence of T-cell and macrophage infiltrates
- Myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab/nivolumab



- 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

Johnson DB, et al. *N Engl J Med* 2016; 375:1749-55; Laubli H, et al. *J Immunother Cancer* 2017;5:46.

irAEs and Overall Survival

- Data emerging that irAE may be associated with improved survival
- Moffitt Cancer Center study of 148 patients treated with nivolumab plus peptide vaccine or nivolumab alone[1]
  - Statistically significant OS benefit with rash or vitiligo
  - No significant survival differences seen with endocrinopathies, colitis, or pneumonitis in this study
- Massachusetts General Hospital study of 154 patients treated with ipilimumab[2]
  - Statistically significant overall median survival benefit in patients with ipilimumab-induced hypophysitis: 19.4 vs. 8.8 months
- Higher response rate was observed in patients who have had an irAE with nivolumab given for an advanced melanoma[3]

OS = overall survival.

1. Freeman-Keller M, et al. *Clin Cancer Res* 2016;22:886-94; 2. Faje AT, et al. *J Clin Endocrinol Metab* 2014;99:4078-85; 3. Weber JS, et al. *J Clin Oncol* 2015;33 (suppl 15; abstr 9018).

Patient Education

- Detailed information for each immuno-oncologic agent including indications, mechanisms of action, and dosing relevant to the patients' disease
- Toxicity information, including signs, symptoms, and monitoring parameters, organized by organ system
- Patient check-lists
- Side effect monitoring tools

https://www.nccn.org/immunotherapy-tool/pdf/NCCN_Immunotherapy_Teaching_Monitoring_Tool.pdf

Quality of Life, Disease Response, and Patient Selection

Quality of Life Improved or Stable with IO

CheckMate 141 Study: nivolumab vs. single-agent therapy of investigator's choice in recurrent or metastatic HNSCC[1]

- Evaluation using EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D-3L
- Improved or stable QOL scores following treatment with single-agent nivolumab

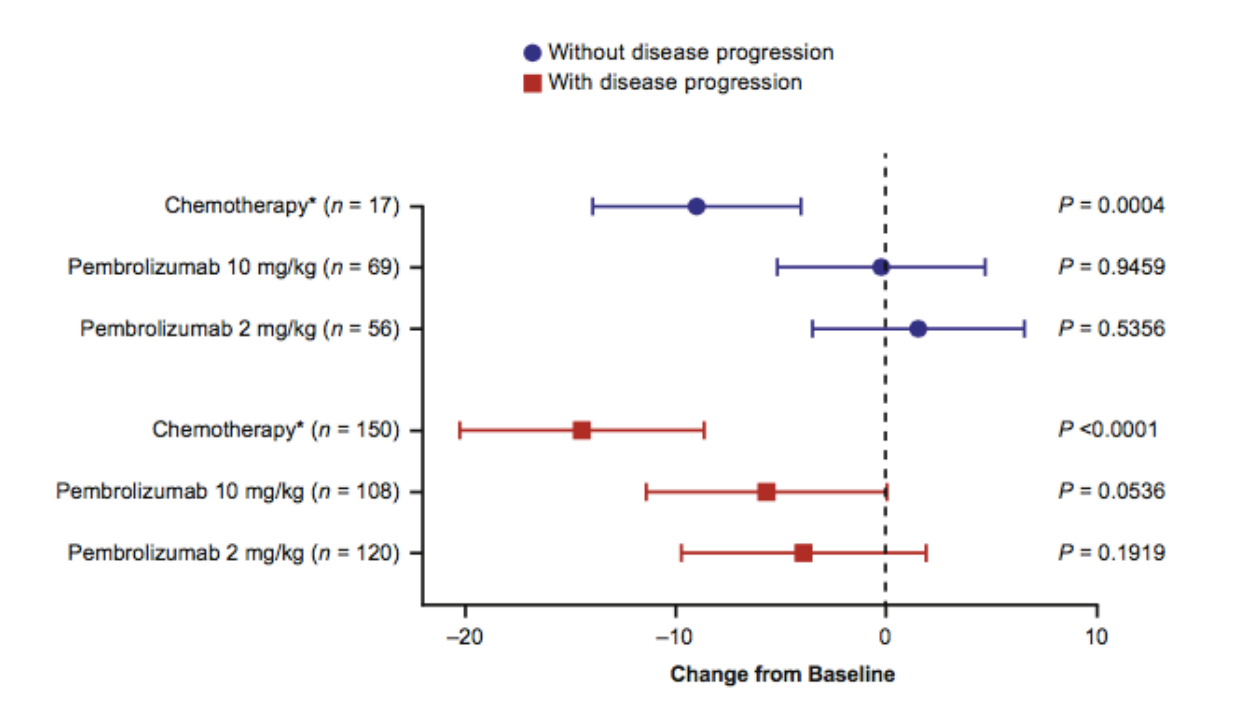
EORTC 18071 Study: adjuvant ipilimumab for melanoma[2]

- EORTC QLQ-C30 questionnaire utilized in this study was **similar** between ipilimumab and placebo groups
- Treatment was discontinued in 50% of patients due to drug-related adverse events

EORTC = European Organisation for Research and Treatment of Cancer; IO = immuno-oncology; QOL = quality of life.

1. Harrington KJ, et al. *Lancet Oncol* 2017;18:1104-15; .2. Lorigan P, et al. *Nat Rev Clin Oncol* 2017;14:395-6.

Pembrolizumab in Melanoma: KEYNOTE-002 QOL



Shadendorf D et al. *Eur J Cancer* 2016;67:46-54.

QOL: Are We Answering the Question?

- Checkpoint inhibitors have a different side-effect profile than chemo, and therefore standard instruments may not address symptoms fully
    - For example, skin problems are not addressed in EORTC QLQ-H&N35 but rash and pruritus were noted more frequently in the nivolumab group than standard therapy
- Patients with advanced disease and poor QOL often drop out of study sooner than those with better QOL
- Current standardized tools may not be accurately measuring QOL in IO
- Further QOL research is needed as the indications for IO continue to grow

Singer S. *Lancet Oncol* 2017;18:993-4.

Responses to Immune Checkpoint Inhibitors Are Different From Chemotherapy

- Checkpoint inhibitors must induce an effective immune response
  - Median time to response 8–12 weeks
  - Assess for response every 12 weeks
- Patterns of response may differ from standard response criteria
  - Prolonged stable disease followed by regression
  - Initial response and slowly over time achieve a complete remission
  - Initial progressive disease followed by a long period of stable disease or regression
    - Tumor growth occurs while immune system is priming for an antitumor response
  - Pseudoprogression: “tumor flare” due to infiltration of tumors by activated immune cells mimic progression

Hodi FS, et al. *J Clin Oncol* 2016;34:1510-7; Atkins MB, et al. *Ann Oncol* 2017;35:117-8.

Patients May Respond to Treatment Beyond Progression

- The patterns of response represent a challenge as they are only discernible in retrospect
  - Disease progression should be confirmed with a repeat scan at least 4 weeks later
- Some patients with initial disease progression that have clinical benefit will ultimately respond to therapy if it is continued beyond initial disease progression
  - CheckMate 025 study: advanced renal cell carcinoma treated with nivolumab
  - 48% of patients with progressive disease by RECIST criteria were treated beyond progression (at least 4 more weeks)
  - 13% of patients had 30% or more decreased tumor burden
  - Median OS for patients treated beyond progression: 28.1 months vs. 15.3 months for patients not treated beyond progression
- Patients who are symptomatically "doing well" may continue therapy beyond disease progression in hope of a delayed response
- On the other hand, decisions to treat beyond disease progression may result in the prolongation of futile treatment

RECIST = Response Evaluation Criteria in Solid Tumors.

Escudier B, et al. *Eur Urol* 2017;72:368-76.

Pre-Existing Autoimmune Disorders Are Not a Contraindication to Immunotherapy

Patients with autoimmune disorders were excluded from the clinical trials, so it has been unclear if it is safe to use immune checkpoint inhibitors

- Recent data suggest that patients with pre-existing autoimmune disease can be treated safely with immune checkpoint inhibitors
- ~ 50% of patients were treated with active autoimmune disease on concomitant treatment (corticosteroids, DMARDs, and/or biologics) for their autoimmune disease
- ~ 30%–40% developed de novo irAE
  - Some had to discontinue therapy but irAE resolved with treatment
- ~30%–40% had exacerbation of the pre-existing autoimmune disease
- ~40%–50% had no autoimmune disease flares or irAEs
- ~20%–30% had an objective response (similar to patients without autoimmune disorders)

DMARDs = disease-modifying antirheumatic drugs.

Abdel-Wahab N, et al. *Arthritis Rheumatol* 2016;68(suppl 10); Johnson DB, et al. *JAMA Oncol* 2016;2(2):234-40; Menzies AM, et al. *Ann Oncol* 2017;28;368-76.

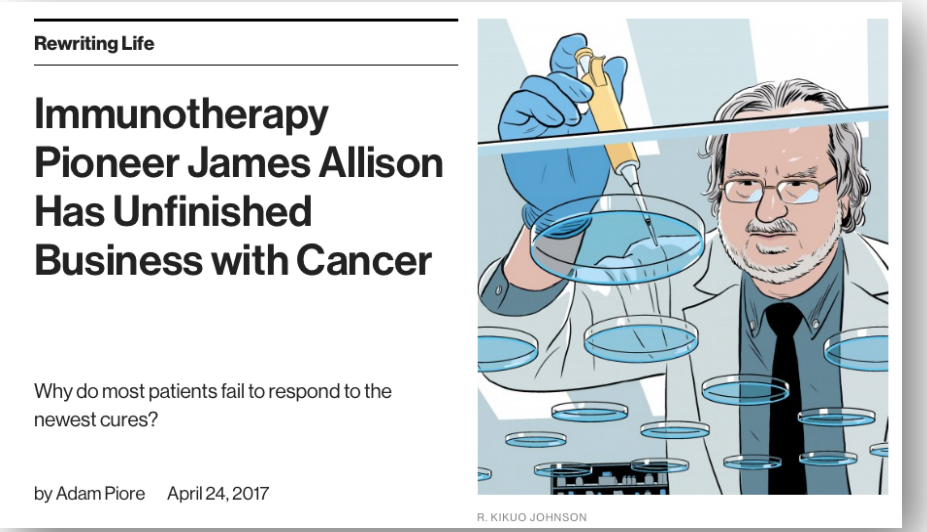
Common Questions

- What if prednisone isn't effective in managing the adverse effect?
  - Is the steroid adequately dosed?
  - Consider hospitalization and infliximab (except not for hepatitis) or mycophenolate mofetil
- Should we premedicate infusions with steroids?
  - Not recommended
- Should we modify doses to alleviate irAEs?
  - Dose modification is not recommended; delay or discontinue IO
- Will giving patients corticosteroids limit efficacy of the immunotherapy?
  - Data from clinical trials do not suggest steroids limit efficacy of the immunotherapy[1]

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

Future Directions

- Over 3,000 ongoing IO trials
  - New targets
  - Combination therapies
  - Sequencing trials
  - Dose duration trials
- Major investigative questions
  - What is the immune response doing that leads to tumor rejection?
  - What is the immune response doing that it stops rejecting the tumor and it starts growing again?



Rewriting Life

Immunotherapy Pioneer James Allison Has Unfinished Business with Cancer

Why do most patients fail to respond to the newest cures?

by Adam Piore April 24, 2017

R. KIKUO JOHNSON

Piore, A. James Allison Has Unfinished Business with Cancer, *MIT Technology Review,* 2017, https://www.technologyreview.com/s/604086/immunotherapy-pioneer-james-allison-has-unfinished-business-with-cancer.

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