ADVANCES IN Cancer IMMUNOTHERAPY™

Management and Mitigation of irAEs for Immunotherapy Prescribers

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- Consulting Fees and honoraria
  - BMS, Merck, Genentech, Merck KGA
- Research Support
  - Astrazeneca/Medimmune
- I will not be discussing non-FDA approved indications during my presentation.

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Case Study #1

- A 66-year-old male previously treated mRCC enrolled in a clinical trial of anti-PD-L1 Ab therapy
- Approximately two weeks after his second dose of anti-PD-L1 antibody, he presented with sudden onset of double vision, along with a 10-day history of muscle pain and weakness, joint aches and generalized malaise.
- Neurologic exam was notable for near complete opthalmoplegia, fatigability of his deltoids, otherwise non-focal. Labs were notable for transaminitis and myositis.

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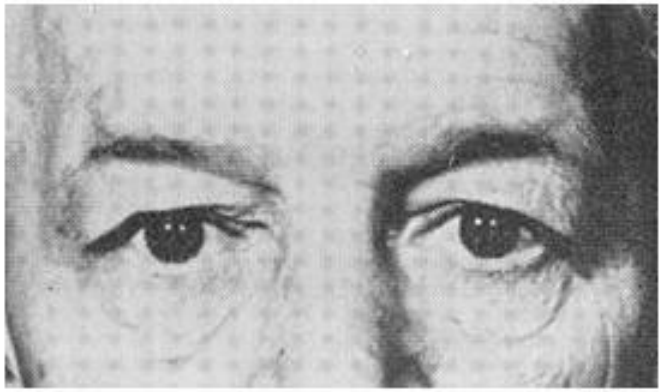
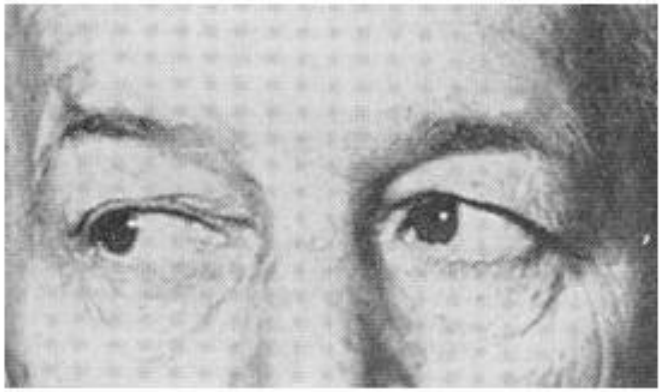
"Look at me"



"Look to the right"



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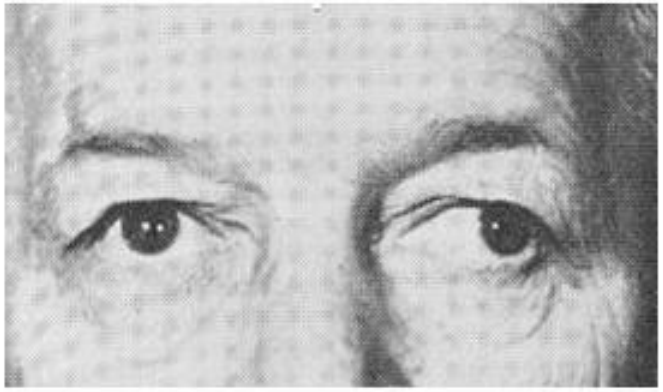

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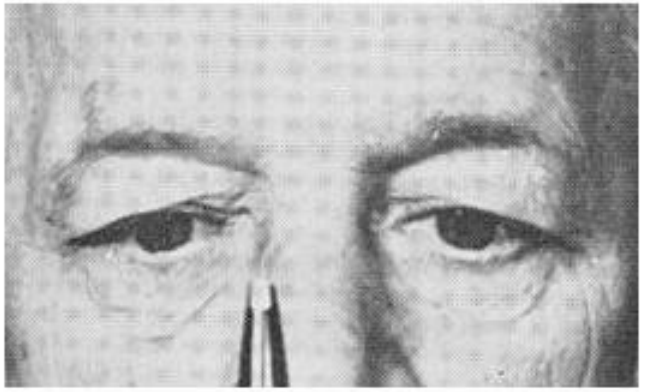

http://www.etsu.edu/com/medicalmystery/IOP.aspx

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Case Description: 66-Year-Old Male (continued)

- This patient was diagnosed with drug-induced myasthenia gravis by serologic testing:
  - Clinical trial related labs: Antibody titer detected in pretreatment sample at lower level.

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Case Description: 66-Year-Old Male (continued)

- Neurologic symptoms resolved on steroids.
- Patient was taken off study, then developed disease progression three months later.
- Patient subsequently received VEGF TKI therapy.

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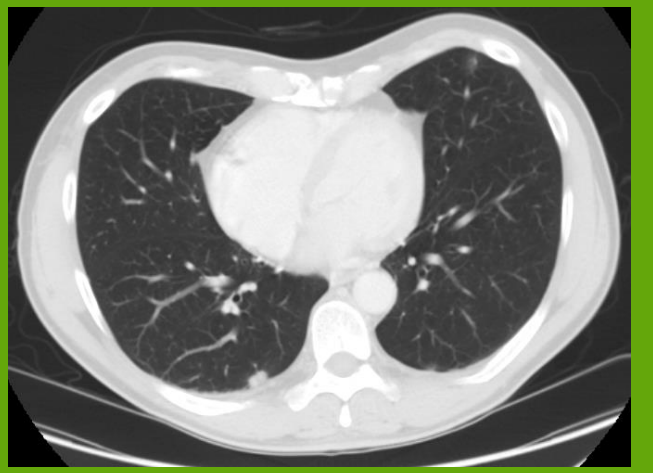
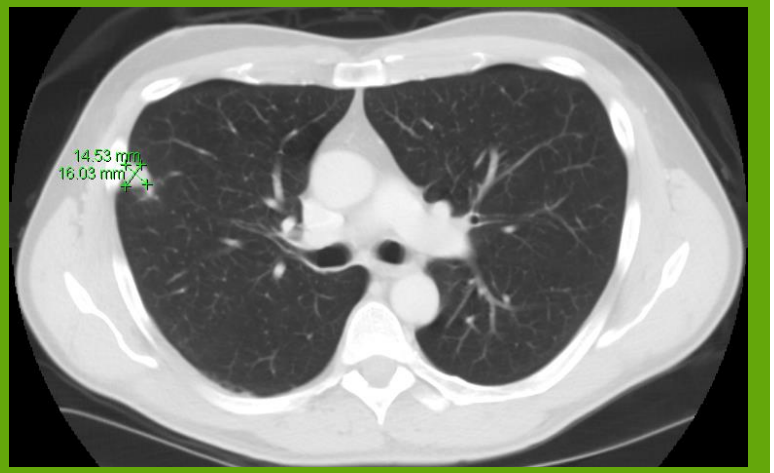
Case Study #2

- A 56-yr-old male with stage 4 RCC was treated with high dose IL-2
- After progression, he was enrolled in clinical trial for nivolimab at 3 mg/kg
  - Patient developed a dry cough and came in for an exam

Scan at Mo 6



Subsequent Scan at Mo 8



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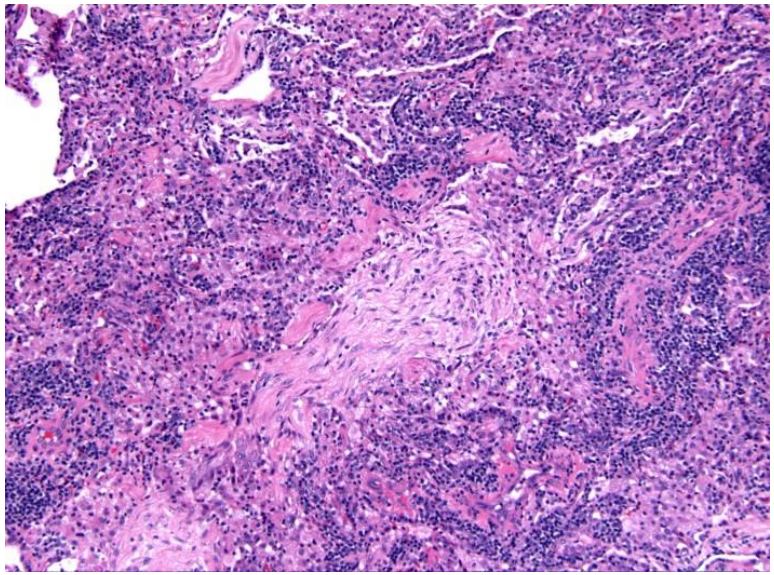
Case Study #2

- Patient underwent biopsy to confirm disease progression
  - Biopsy suggested bronchiolitis obliterans



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Patient underwent biopsy to confirm disease progression, and the biopsy suggested bronchiolitis obliterans.

How would you manage this patient?

1. Continue nivolumab and start steroid treatment.
2. Continue nivolumab and start broad-spectrum antibiotics.
3. Discontinue nivolumab and start steroid treatment.
4. Discontinue nivolumab and start broad-spectrum antibiotics.

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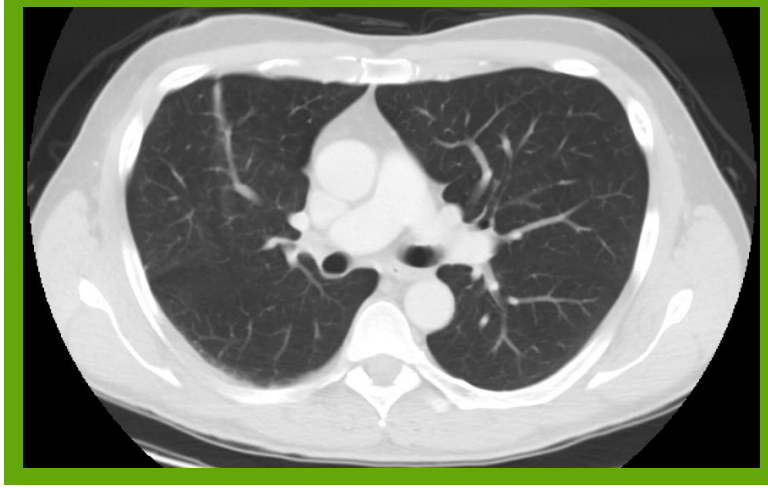
Case Study #2

- Symptoms and lung lesions resolved with initiation of steroid therapy
- Nivolumab treatment was discontinued, and disease is currently stable off all therapy x two years

Lung Lesions Resolved



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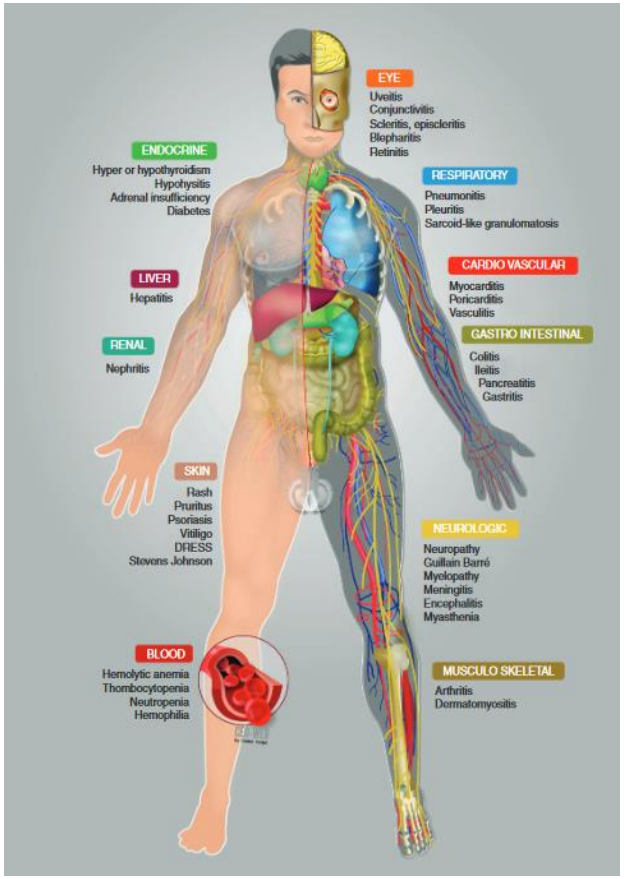
Spectrum of toxicity of immune checkpoint blockade



Champlat, Ann Oncol (2016) 27 (4): 559-574

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General principals of immunotherapy toxicity management

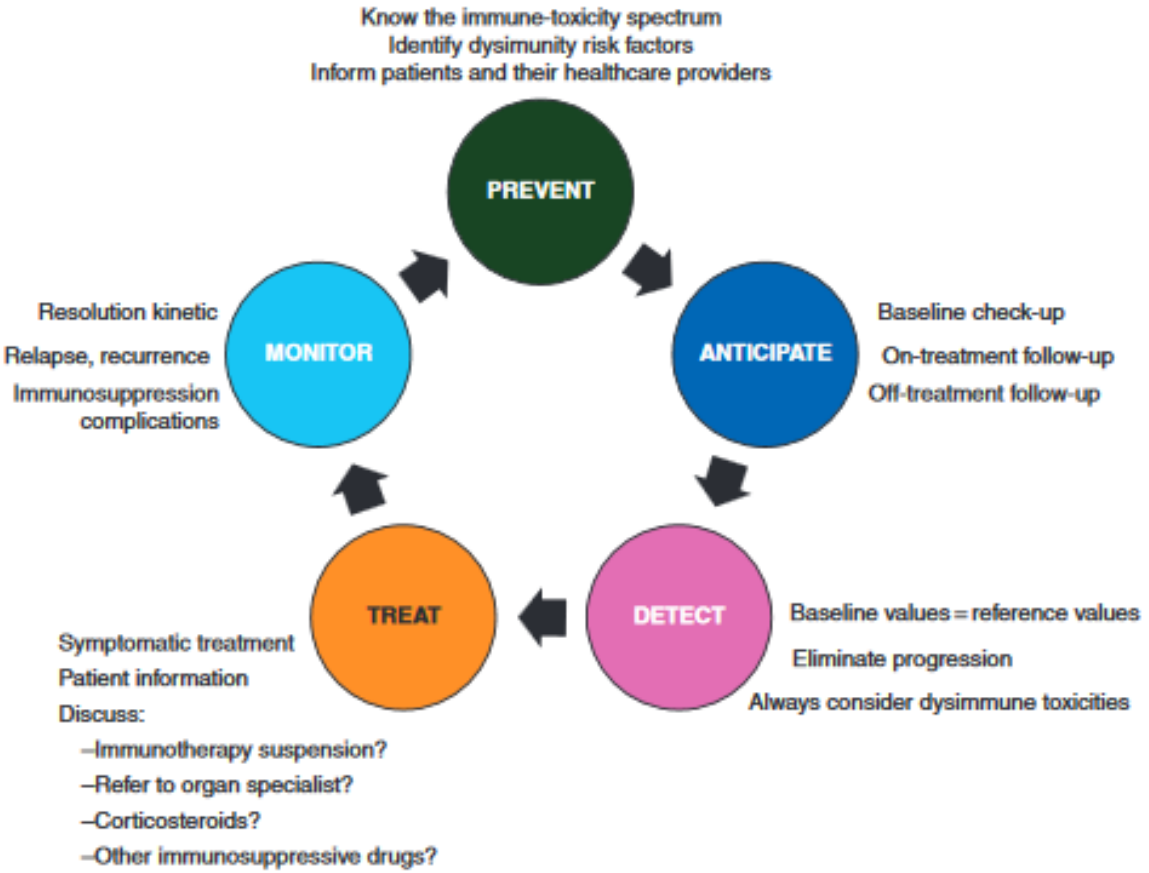

Figure 1. The five pillars of immunotherapy toxicity management.

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Prevention

- Assess for personal and family history of autoimmune diseases.
  - digestive (Crohn's disease, ulcerative colitis, celiac disease),
  - skin (psoriasis)
  - Rheumatic (spondyloarthritis, rheumatoid arthritis, lupus)
  - endocrine (diabetes, thyroiditis)
  - respiratory (interstitial pneumonitis, sarcoidosis),
  - pancreatic (pancreatitis)
  - kidney (nephritis)
  - Hematological (hemolytic anemia, immunologic thrombocytopenic purpura),
  - neurological (myasthenia, multiple sclerosis)
  - eye (uveitis, scleritis,retinitis)
  - cardiovascular (heart failure, left ventricular systolic dysfunction, myocarditis, vasculitis)
- Chronic infections (Hepatitis B?)
- Chronic medications/exposures associated with autoimmune diseases
- Sites of disease where immune response may increase symptoms (lymphangitic spread)

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Informing other specialists: Patient card

Name, Family name:
Immunotherapy drug(s):
I am currently receiving an immunotherapy which may increase the risk of occurrence of autoimmune diseases and in particular:

- pneumonitis (inflammation of the lungs)
- colitis (inflammation of the gut)
- hepatitis (inflammation of the liver)
- nephritis (inflammation of the kidneys)
- endocrinopathy: hypophysitis, thyroid dysfunction, diabetes, adrenal insufficiency (inflammation of the hormone producing organs)
- cutaneous rash (inflammation of the skin)

as well as other immune-related adverse events: neurological, hematological, ophthalmological,... **The management of these dysimmune adverse events is specific and sometimes urgent. It absolutely requires coordination with the health care team which has prescribed the treatment:**
Prescriber ID and contact information (reported at the back of this card)

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Awareness: Baseline

Table 2. Immunotherapy baseline checklist

Physical examination
Performance status
Weight, size, body mass index
Heart rate and blood pressure
General symptoms such as asthenia or appetite should be evaluated as they are frequently affected
Particularly pay attention to pre-existing symptoms regarding: intestinal transit, dyspnea and coughing, rash, nausea, headaches, signs of motor or sensory neuropathy and arthralgia
History of fever or recent infection must be checked and investigated appropriately
Baseline electrocardiogram
Ongoing treatment
Laboratory test
Complete CBC
Serum electrolytes: Na, K, alkaline reserve, calcium, phosphorus, uric acid, urea, creatinine with estimated GFR (MDRD or CKD EPI)
Glycemia
Total bilirubin, AST, ALT, GGT, PAL
Albuminemia, CRP
TSH, T4
Cortisol and ACTH at 8 am
LH FSH estradiol testosterone
Proteinuria: morning sample, fasting if possible (g/l with concomitant dosing creatinine in mmol/l)—better than an urine dipstick to detect low levels of proteinuria and tubular proteinuria
Urinary sediment
Quantiferon tuberculosis or TST in case of anterior exposure
Virology: HIV, HCV and HBV serology
Antibody: ANA, TPO Ab, Tg Ab
If doable, we recommend a plasma/serum biobanking before the beginning of immunotherapy to retrospectively titrate at baseline any other factor of interest in case of development of toxicity with biological marker.
Imaging
X-ray chest imaging reference is recommended at baseline
The conventional pretherapeutic thoracic CT scan should be performed with thin sections with and without injection to have a baseline reference in case a pulmonary toxicity occurs.
Any other evaluation may also be necessary before starting immunotherapy depending on patient's history, symptoms or diseases detected at baseline.

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Overview of toxicity of checkpoint blockade

Type of Immunotherapy	General Symptoms	Skin Toxicity	GI Toxicity	Hepatotoxicity	Endocrinopathy	Other Toxicities
Checkpoint protein inhibition: CTLA-4	Fevers, chills, and lethargy[62]	Maculopapular[62]	Diarrhea and colitis with ulceration[62]	Elevated LFTs[62]	Hypophysitis, thyroiditis, and adrenal insufficiency[62]	Neuropathy, nephritis, Guillain-Barré, myasthenia gravis, sarcoid, and thrombocytopenia all rare[62,63]
Checkpoint protein inhibition: PD-1	Fevers, chills, and lethargy[68-72]	Maculopapular[68-72]	Diarrhea and colitis with ulceration: uncommon[68-72]	Elevated LFTs uncommon[68-72]	Hypophysitis, thyroiditis more common, adrenal insufficiency[68-72]	Pneumonitis not common; neuropathy, Guillain-Barré, myasthenia gravis, nephritis, all rare[68-72]
Checkpoint protein inhibition: PD-L1	Fevers, chills, and lethargy[81,82]	Maculopapular[81,82]	Diarrhea and colitis with ulceration: rare[81,82]	Elevated LFTs rare[81,82]	Hypophysitis, thyroiditis more common, adrenal insufficiency[81,82]	Pneumonitis rare; anemia rare[81,82]
Combination checkpoint protein inhibition	Fevers, chills, and lethargy[100]	Maculopapular[100]	Diarrhea and colitis with ulceration; pancreatic lab elevation common[100]	Elevated LFTs common[100]	Hypophysitis, thyroiditis more common, adrenal insufficiency[100]	Pneumonitis not common[100]; neuropathy, Guillain-Barré, myasthenia gravis, nephritis, all rare[100]

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Toxicities vary by drug regimen

More toxicity with Nivolumab/Ipilimumab

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

Larkin, N Engl J Med 2015;373:23-34.

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General management of checkpoint blockade toxicity

Table 4. Typical management of irAEs

Severity—CTCAE grade	Ambulatory versus inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day	Not recommended	Suspend temporarily[a]
3	Hospitalization	Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ Specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization consider intensive care unit	Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ specialist referral advised	Discontinue permanently

Some dysimmune toxicities may follow a specific management: this has to be discussed with the organ specialist.
[a]Outside skin or endocrine disorders where immunotherapy can be maintained.

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Skin toxicity

Events	Dose Modification		Toxicity Management
Rash (Excluding Bullous Skin Formations)	Any Grade		• Monitor for signs and symptoms of dermatitis (rash and pruritus) • **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED**
	Grade 1	No dose modification	For Grade 1: • Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream)
	Grade 2	For persistent (> 1 to 2 weeks) Grade 2 events, hold scheduled study drug/regimen until resolution to ≤ Grade 1 or baseline. • If toxicity worsens, treat as Grade 3 • If toxicity improves, resume study drug/regimen administration at next scheduled dose	For Grade 2: • Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream) • Consider moderate-strength topical steroid • If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening, discuss with study physician and consider systemic steroids prednisone 0.5 to 1 mg/kg/day or IV equivalent ◦ Consider dermatology consult ◦ Consider skin biopsy if persistent for > 1 to 2 weeks or recurs
	Grade 3	• Hold study drug/regimen until resolution to ≤ Grade 1 or baseline • If temporarily holding study drug/regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue study drug/regimen	For Grade 3 or 4: • Discuss with study physician • Consider hospitalization • Monitor extent of rash (Rule of Nines) • Consult dermatology • Consider skin biopsy (preferably more than 1) as clinically feasible. • Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics
	Grade 4	Permanently discontinue study drug/regimen	

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Diarrhea/ Enterocolitis

Diarrhea/ Enterocolitis	Any Grade		• Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits) • Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections) • Steroids should be considered if an alternative etiology is not determined, even for low-grade events, in order to prevent potential progression to higher grade event • Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1	No dose modification	For Grade 1: • Close monitoring for worsening symptoms • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide

Events	Dose Modification		Toxicity Management
	Grade 2	Hold study drug/regimen until resolution to ≤ Grade 1 • If toxicity worsens, treat as a Grade 3 or Grade 4 • If toxicity improves to baseline, treat at next scheduled treatment date	For Grade 2: • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide • If event is persistent (> 3 to 5 days) or worsens, consider prednisone 0.5 to 1 mg/kg/day or IV equivalent • If not responsive within 3 to 5 days, consider IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day If not responsive within 3 to 5 days or worsens, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day • If no improvement within 3 to 5 days, consider further immunosuppressive therapy (eg, infliximab) • Consult study physician if no resolution to ≤ Grade 1 in 3 to 4 days • Once improving, gradually taper steroids over ≥ 4 weeks
	Grade 3 or 4	Permanently discontinue study drug/regimen	For Grade 3 or 4: • Discuss with study physician • Monitor stool frequency and volume, and maintain hydration • Urgent GI consult and imaging as appropriate • Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day • If no improvement within 3 to 5 days, consider further immunosuppressive therapy (eg, infliximab) • Caution: Ensure GI consult to rule out bowel perforation and refer to label before using infliximab • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics

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Endocrinopathies

Events	Dose Modification		Toxicity Management
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency)	Any Grade		• Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. • Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, infections) • Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs dependent on suspected endocrinopathy • If a subject experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1	No dose modification	For Grade 1 (Including Those with Asymptomatic TSH Elevation): • Monitor subject with appropriate endocrine function tests • If TSH < 0.5 × LLN, or TSH > 2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult
	Grade 2	Hold study drug/regimen dose until resolution to ≤ Grade 1 • If toxicity worsens, treat as a Grade 3 or Grade 4 event • If toxicity improves to baseline, treat at next scheduled treatment date	For Grade 2 (including those with symptomatic endocrinopathy): • Discuss with study physician • Initiate hormone replacement as needed for management • Evaluate endocrine function, and as clinically indicated, consider pituitary scan • For subjects with abnormal endocrine work up, consider short-term, high-dose corticosteroids (eg, methylprednisolone or IV equivalent) with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones) • For subjects with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated

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Hepatic events

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

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Managing complications of immunosuppression

- Corticosteroid termination should follow a gradual decrease of doses over a period of at least 1 month.
- Consider antibiotic prophylaxis with trimethoprim/sulfamethoxazole (400 mg po qd) if corticosteroids ≥1 mg/kg are used.
  - Prophylaxis continued until steroid dose is below 10 mg per day.
- Consider testing patients for tuberculosis (quantiferon or TST) in case of severe toxicity requiring additional immunosuppressive drugs and introduce anti-tuberculosis prophylaxis if positive.

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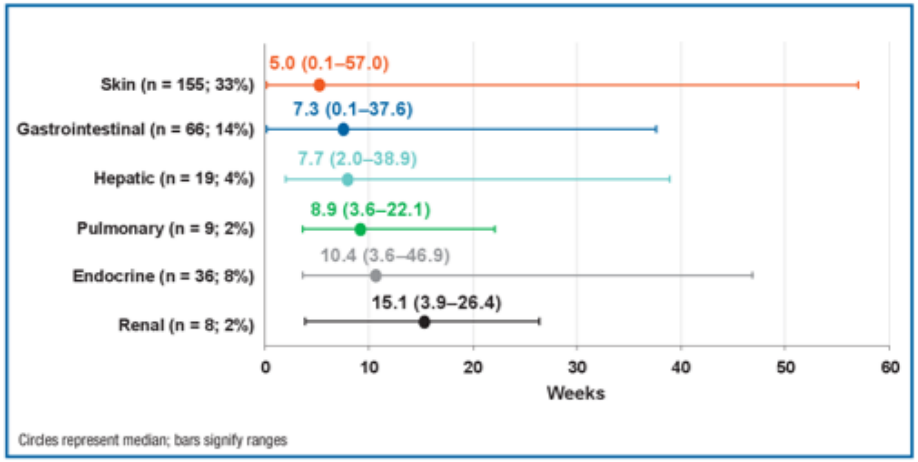
Time to onset and resolution of

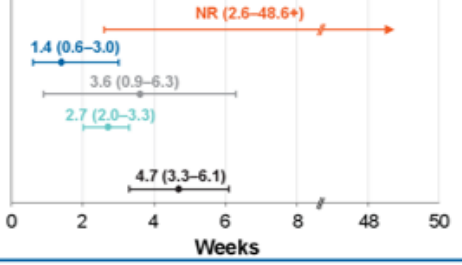
Figure 1. Time to onset of select treatment-related AEs (any grade; N = 474)



Some thyroid function may be restored over time
Dysfunction of the corticosteroid and gonadal axes is likely permanent

Figure 4. Time to resolution of select treatment-related AEs with IMs (grade 3–4)

	Grade 3–4, n	Cases resolved, n (%)
Skin	2	1 (50%)
Gastrointestinal	5	5 (100%)
Endocrine	2	2 (100%)
Hepatic	2	2 (100%)
Pulmonary	0	0
Renal	2	2 (100%)



Circles represent median; bars signify ranges
NR = not reached

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Are toxicities associated with outcome ?

Ipilimumab: YES

Table 5. Relationship between IRAEs and response

	All	NR	PR + CR	*P*	Duration of response (mo), median (range)
IRAE					
None	53	52	1 (2%)	0.0004	18+
Only grade 1/2	36	28	8 (22%)		11 (4-30+)
Grade 3/4	50	36	14 (28%)		35 (7-53+)

Downey, Clin Cancer Res 2007;13:6681

Nivolumab: ?

	Nivo overall	Any Grade irAE	GR 3-4 irAE
ORR	31%	48.6%	27.8%

Weber J, ASCO 2015; Abstr 9018

Is clinical benefit affected by steroids/immune modulators ?

Ipilimumab: No

Table 6. Duration of response in patients requiring steroid administration

	No. patients	Duration of response	Median (mo)	*P*
All responders	23		30.6	
Requiring steroids	12	6, 7, 9, 10, 11, 19, 28+, 29+, 31+, 43, 47+, 52+	19.3	0.23*
Not requiring steroids	11	4, 5, 6, 10, 17+, 17+, 18+, 22+, 30+, 50+, 53+	Not reached	

*By time-varying covariate analysis.

Downey, Clin Cancer Res 2007;13:6681

Nivolumab: No

Table 4. Response in pts who received or did not receive a systemic IM

	NIVO monotherapy with IM N = 139	NIVO monotherapy without IM N = 437
ORR, n (%), [95% CI]	40 (28.8) [21.4–37.1]	141 (32.3) [27.9–36.9]
BOR, n (%)		
CR	7 (5.0)	22 (5.0)
PR	33 (23.7)	119 (27.2)
SD	31 (22.3)	102 (23.3)
PD	63 (45.3)	173 (39.6)
Not evaluable	5 (3.6)	21 (4.8)
Median duration of response, mo (95% CI)	NR (9.3–NR)	22.0 (22.0–NR)
Median time to response, mo (range)	2.1 (1.2–8.8)	2.1 (1.4–9.2)

Pts evaluable for response had a baseline tumor assessment and a confirmatory scan at least 4 weeks after the first documented response
BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease

Weber J, ASCO 2015; Abstr 9018

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PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

- **Will toxicity management prove challenging?**
  - **Will rare but serious toxicities occur?**
  - Will late toxicity emerge?
  - Will certain toxicities make combinations difficult?
  - Will history of autoimmunity limit application?

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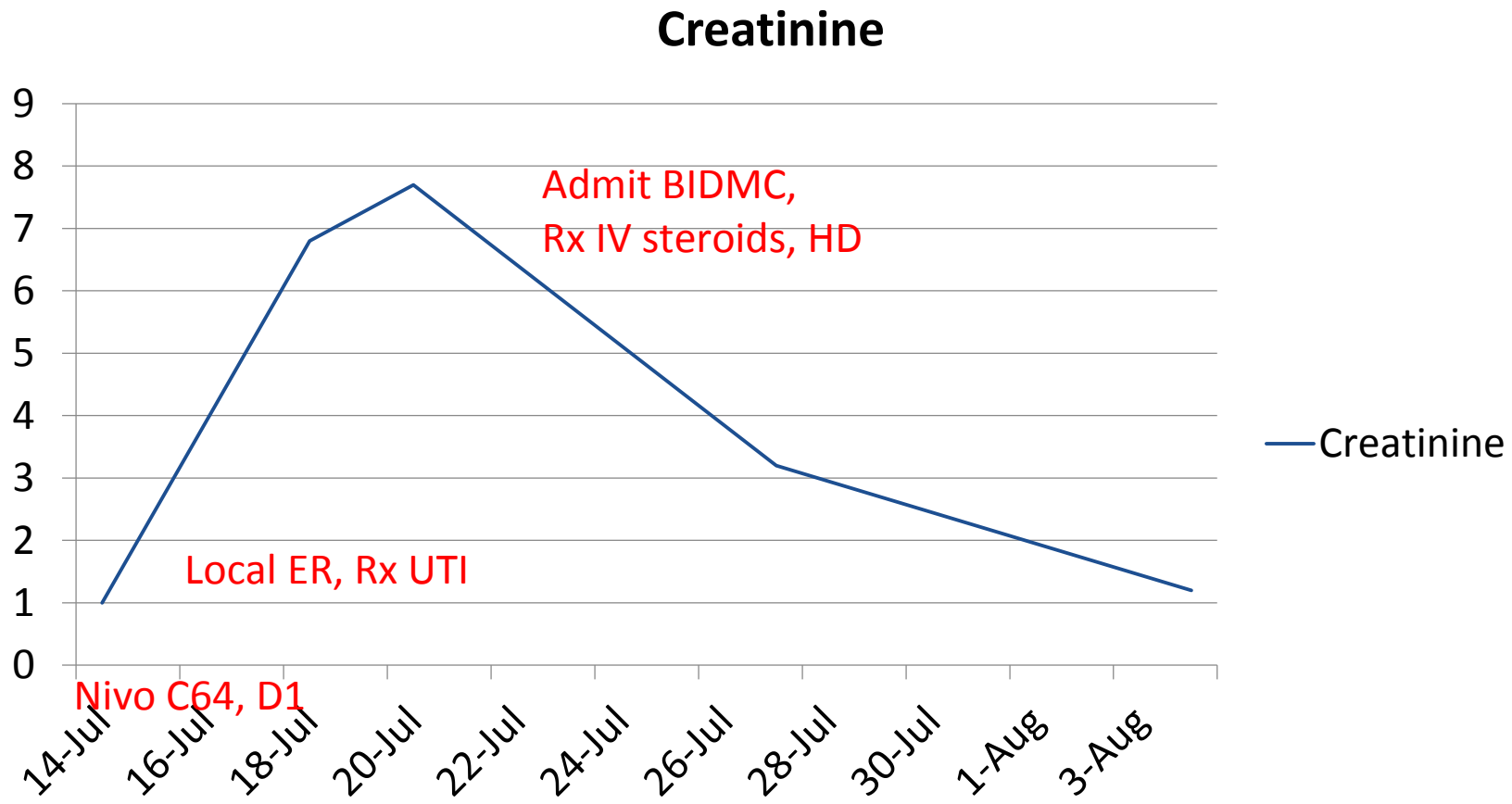
Late PD-1 Toxicity?: Acute Renal Failure



74 yo female, mRCC, s/p sunitinib, enrolled in Nivo P2 trial

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  - Will late toxicity emerge?
  - **Will certain toxicities make combinations difficult?**
    - (e.g. nephritis, hepatitis, pneumonitis)
  - Will history of autoimmunity limit application?

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Table 4. Select Adverse Events and Their Management with Immunomodulatory Medication (IMM), According to Organ Category.

Organ Category	Nivolumab plus Ipilimumab (N=94)				Ipilimumab (N=46)			
	Reported Adverse Event	Treatment with IMM	Resolution of Event after Treatment with IMM	Median Time to Resolution	Reported Adverse Event	Treatment with IMM	Resolution of Event after Treatment with IMM	Median Time to Resolution
	no. of patients	*no. of patients/total no. (%)*		*wk (95% CI)*	*no. of patients*	*no. of patients/total no. (%)*		*wk (95% CI)*
Skin								
Any grade	67	41/67 (61)	24/35 (69)	18.6 (9.3–35.1)	26	13/26 (50)	11/13 (85)	8.6 (3.3–22.0)
Grade 3 or 4	9	9/9 (100)	8/9 (89)	6.1 (0.9–24.1)	0	0	0	NE
Gastrointestinal								
Any grade	48	31/48 (65)	[illegible]	4.7 (3.0–6.7)	17	11/17 (65)	7/9 (78)	5.0 (1.4–12.1)
Grade 3 or 4	20	17/20 (85)	15/17 (88)	4.3 (1.4–10.7)	5	5/5 (100)	4/5 (80)	3.6 (0.7–5.0)
Endocrine†								
Any grade	32	14/32 (44)	2/14 (14)	NE (NE–NE)	8	3/8 (38)	1/3 (33)	NE (0.9–NE)
Grade 3 or 4	5	4/5 (80)	1/4 (25)	NE (5.6–NE)	2	2/2 (100)	1/2 (50)	NE (0.9–NE)
Hepatic								
Any grade	26	13/26 (50)	11/13 (85)	14.1 [illegible]	2	0/2	0	NE
Grade 3 or 4	14	12/14 (86)	10/12 (83)	8.3 (2.1–14.1)	0	0	0	NE
Pulmonary								
Any grade	11	8/11 (73)	6/8 (75)	6.1 (0.3–9.0)	2	2/2 (100)	2/2 (100)	3.2 (2.9–3.6)
Grade 3 or 4	3	3/3 (100)	2/3 (67)	9.0 (0.3–9.0)	1	1/1 (100)	1/1 (100)	3.6 (NE–NE)
Renal								
Any grade	3	2/3 (67)	2/2 (100)	0.4 (0.3–0.6)	1	0/1	0	NE
Grade 3 or 4	1	1/1 (100)	1/1 (100)	0.6 (NE–NE)	0	0	0	NE

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PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

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  - Will certain toxicities make combinations difficult?
  - **Will history of autoimmunity limit application?**

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Original Investigation

Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders

Douglas B. Johnson, MD; Ryan J. Sullivan, MD; Patrick A. Ott, MD, PhD; Matteo S. Carlino, MBBS; Nikhil I. Khushalani, MD; Fei Ye, PhD; Alexander Guminski, MD, PhD; Igor Puzanov, MD; Donald P. Lawrence, MD; Elizabeth I. Buchbinder, MD; Tejaswi Mudigonda, BS; Kristen Spencer, DO; Carolin Bender, MD; Jenny Lee, MBBS; Howard L. Kaufman, MD; Alexander M. Menzies, MBBS; Jessica C. Hassel, MD; Janice M. Mehnert, MD; Jeffrey A. Sosman, MD; Georgina V. Long, MBBS; Joseph I. Clark, MD

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Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders

Table 2. Autoimmune Exacerbations and Grade 3 to 5 Immune-Related Adverse Events

Patient No.	Baseline Condition	Autoimmune Exacerbation	Treatment	Immune-Related Adverse Event	Treatment	Outcome Notes
2	Sarcoidosis	...	...	Glaucoma	Ocular steroids	
3	RA	Joint pain	As for hypophysitis	Hypophysitis	Prednisone 1 mg/kg tapered over 6 wk; now receiving 7.5 mg	Durable CR
4	RA	...	...	Thyroiditis	Prednisone 1 mg/kg tapered over 2 wk	
5	Psoriasis	Worsening plaques	As for colitis	Colitis	Methylprednisolone 2 mg/kg tapered over 6 wk	After 1 dose
6	Psoriasis, Graves disease	...	...	Hypophysitis	Prednisone 30 mg ×1 wk, transition to hydrocortisone over 5 d	PR
8	RA, polymyalgia rheumatica	Joint pain, myalgias	Prednisone 30 mg/d tapered over 1 mo	...	...	After 3 d
9	RA	Joint pain	Prednisone 15 mg/d down to 10 mg	...	...	After 7 mo
11	Transverse myelitis	...	...	Colitis	Prednisone 1 mg/kg tapered over 8 wk	
12	Crohn disease	...	...	Colitis	Methylprednisolone 1 mg/kg tapered over 8 wk	After 1 dose
14	Ulcerative colitis	Diarrhea, disease flare	Infliximab, dexamethasone 2 mg daily[a]	...	...	PR
15	Inflammatory arthritis[b]	Joint pain	As for colitis	Colitis	Prednisone 1 mg/kg tapered over 4 wk, infliximab	...
20	Psoriasis	...	...	Hypophysitis	Prednisone 50 mg ×1 dose, then 5 mg daily	...
23	Sarcoidosis	Hypercalcemia, renal insufficiency	Prednisone 25 mg/d, tapered to 20 mg after 4 wk	...	...	Ongoing SD
24	RA	Joint pain	Prednisone 10 mg/d, now receiving 8 mg/d	...	...	Ongoing PR
28	Psoriasis	...	...	Presumed colitis grade 5	Methylprednisolone 1 mg/kg	Patient died

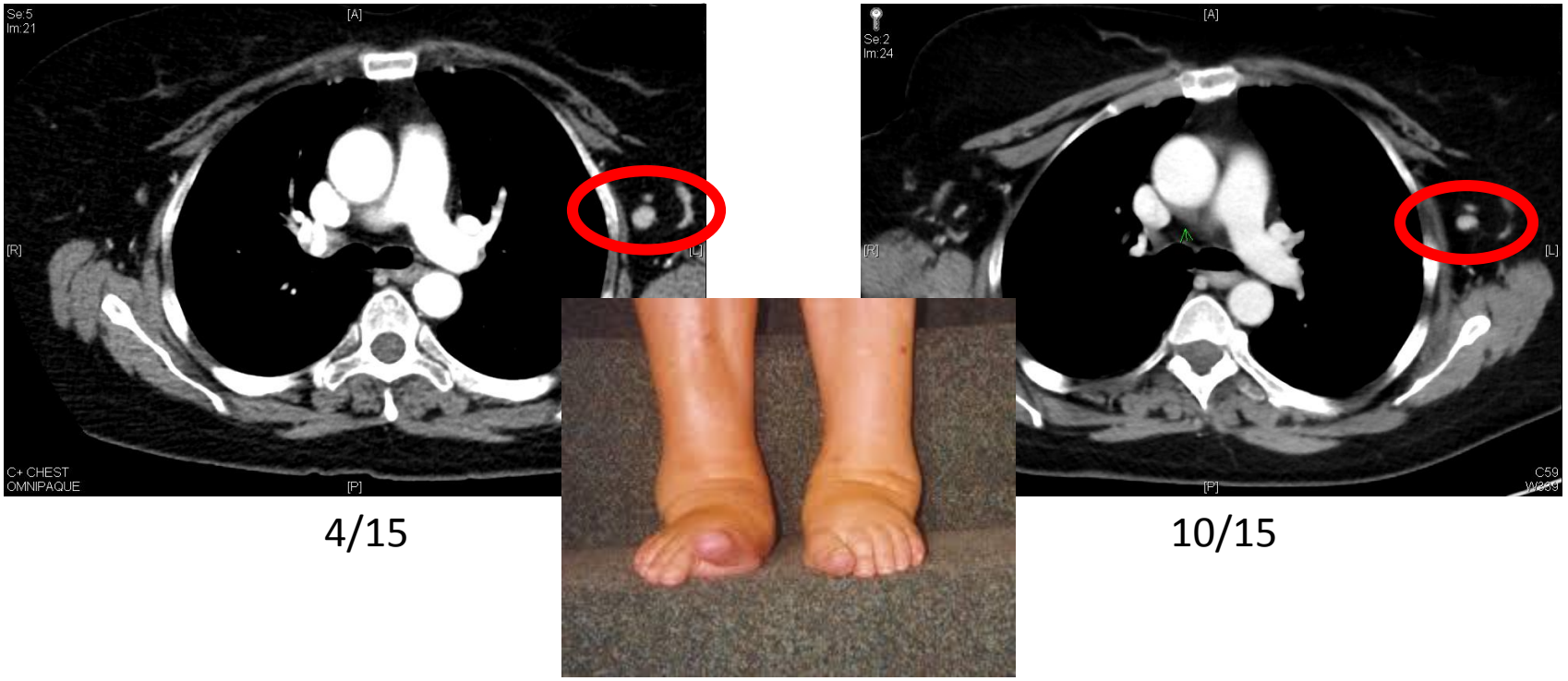
Abbreviations: CR, complete response; ellipses, none; PR, partial response; RA, rheumatoid arthritis; SD, stable disease.

[a] Receiving dexamethasone for brain metastases; infliximab was added with onset of diarrhea.

[b] Patient developed a chronic, inflammatory-appearing arthritis during nivolumab therapy that improved with use of low-dose steroids and hydroxychloroquine.

Johnson et al, JAMA Oncology 2015

PD-1 Blockade in Patient with Autoimmune Disease



4/15

10/15

62 y.o. female, met melanoma, psoriatic arthritis S/P HD IL-2
4/15 - PD-1 (pembro) x 4 doses
7/15 – CTs = SD, PA flared, pembrolizumab held, rx – apremilast
10/15 – CT = MR, PA improved, plan = observation

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Does organ transplant status preclude checkpoint blockade?

- **Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation (**J Immunother Cancer. 2015; 3: 22)
- **Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma** (J Clin Oncol. 2014 Jul 1;32(19))
- Ipilimumab in 30 melanoma patients with autoimmune disease (6 RA, 5 psoriasis, 6 IBD, 2 SLE, 2 MS, 2 autoimmune thyroiditis, 7 others)
  - 43% were receiving immunosuppressive therapy at the time of initiation of ipilimumab therapy, most commonly low-dose prednisone or hydroxychloroquine.
  - 8 patients (27%) experienced exacerbations of their autoimmune condition necessitating systemic treatment; all were managed with corticosteroids
  - Six patients experienced an objective response (20%), including 1 with a durable complete response

JAMA Oncol. 2016 Feb 1;2(2):234-40

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Summary

- Have a high level of suspicion for autoimmune mediated events
  - Very unusual events can occur
  - But include other etiologies in the differential
- Patient education
- Referral to other consultants
- Steroids
- Clinical benefit possible even with steroids

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