Welcome to the Advances in Cancer Immunotherapy™ Post-Program Webinar

With program organizer:

Michael Morse, MD

Duke University Medical Center

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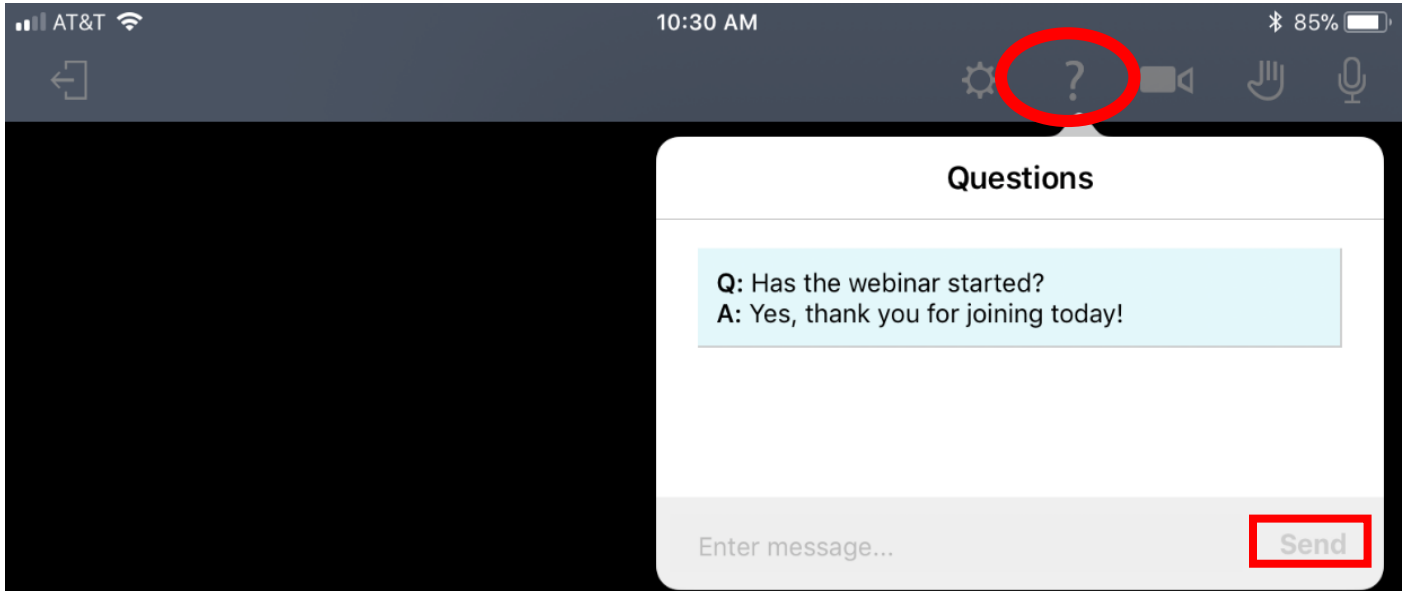
Q&A with Dr. Morse

To submit a question:

Type your question in the Questions box of your webinar panel.

Mobile View



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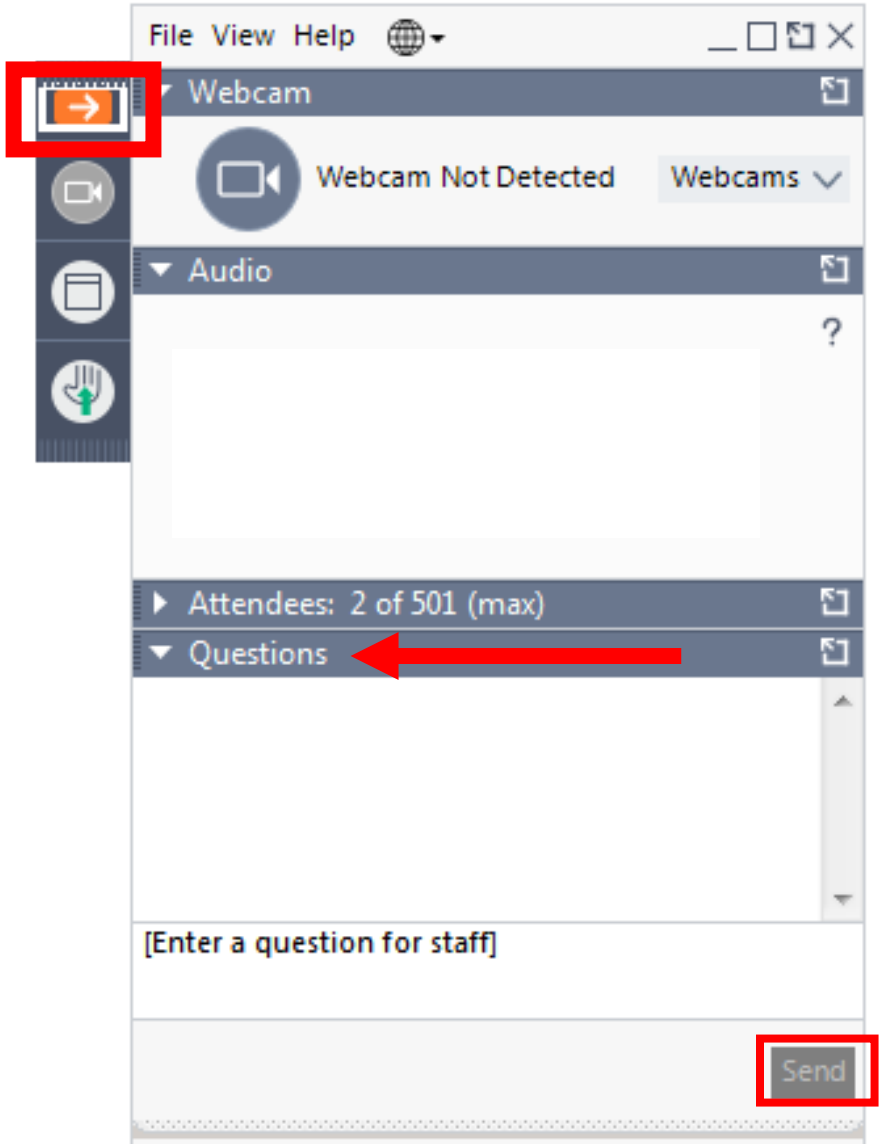

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this webinar is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this webinar should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

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A Deeper Dive into irAEs: A Case Study Example

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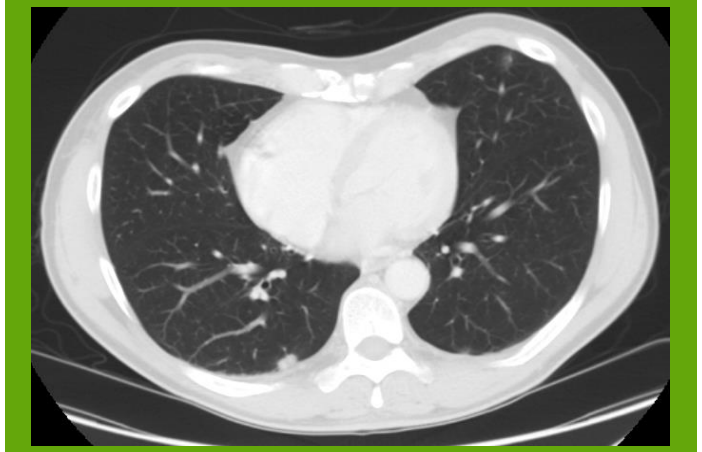
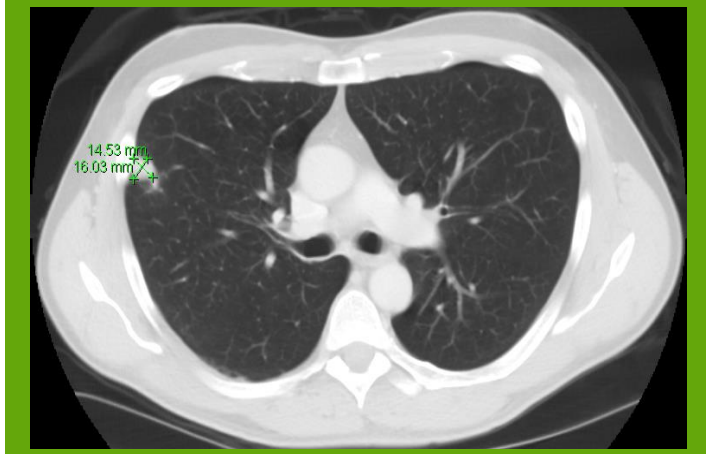
Case Study

- A 56-year-old male with stage IV RCC is treated with sunitinib (HD IL-2).
- After progression, he is enrolled in a clinical trial for nivolimab at 3 mg/kg.
- He develops a dry cough.
- Scans at six and eight months show regression of original tumor, along with a new lesion.

Scan at Mo 6



Subsequent Scan at Mo 8



What would you recommend? (Attendees: Respond via poll question)

a. Continue therapy
b. Switch to VEGF TKI
c. Biopsy to confirm disease progression
d. Start steroid to treat drug-induced lung toxicity

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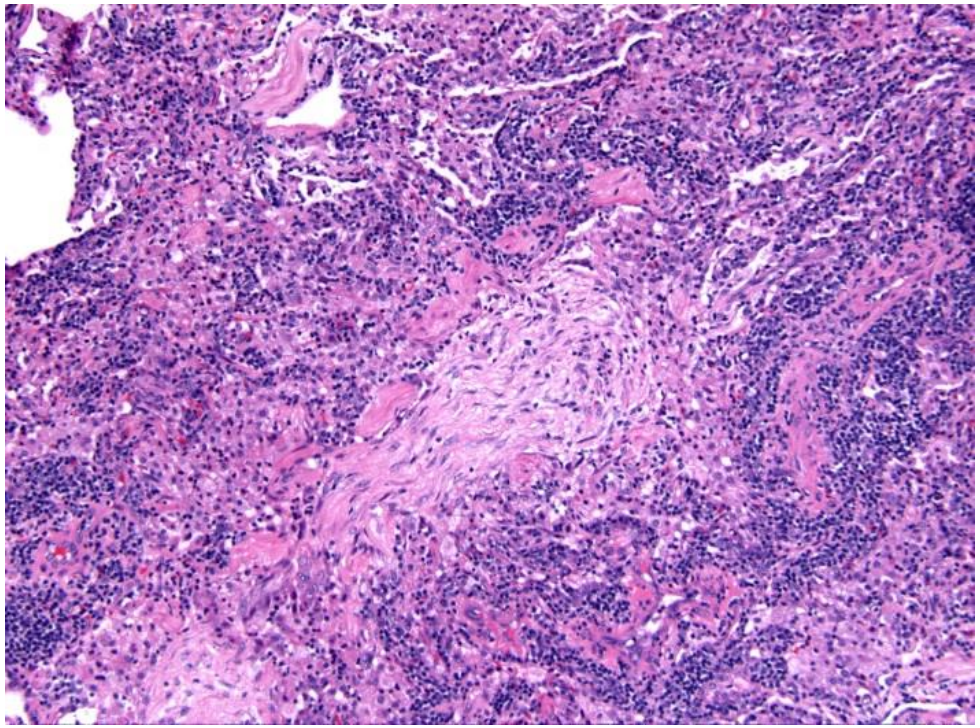
Case Study Continued

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



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Overview of possible mechanisms of irAE

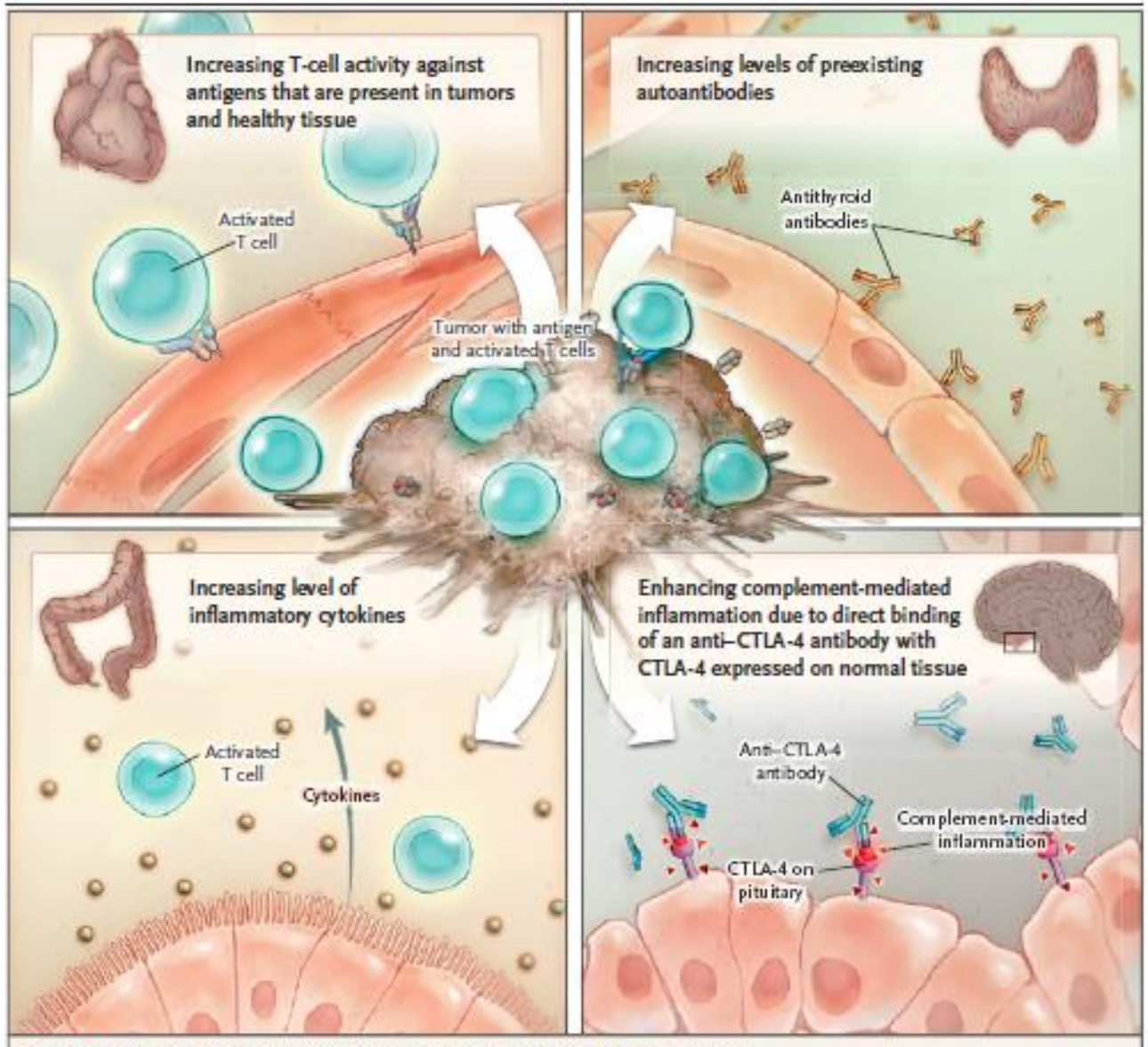

Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.

N Engl J Med. 2018;378(2):158-168.

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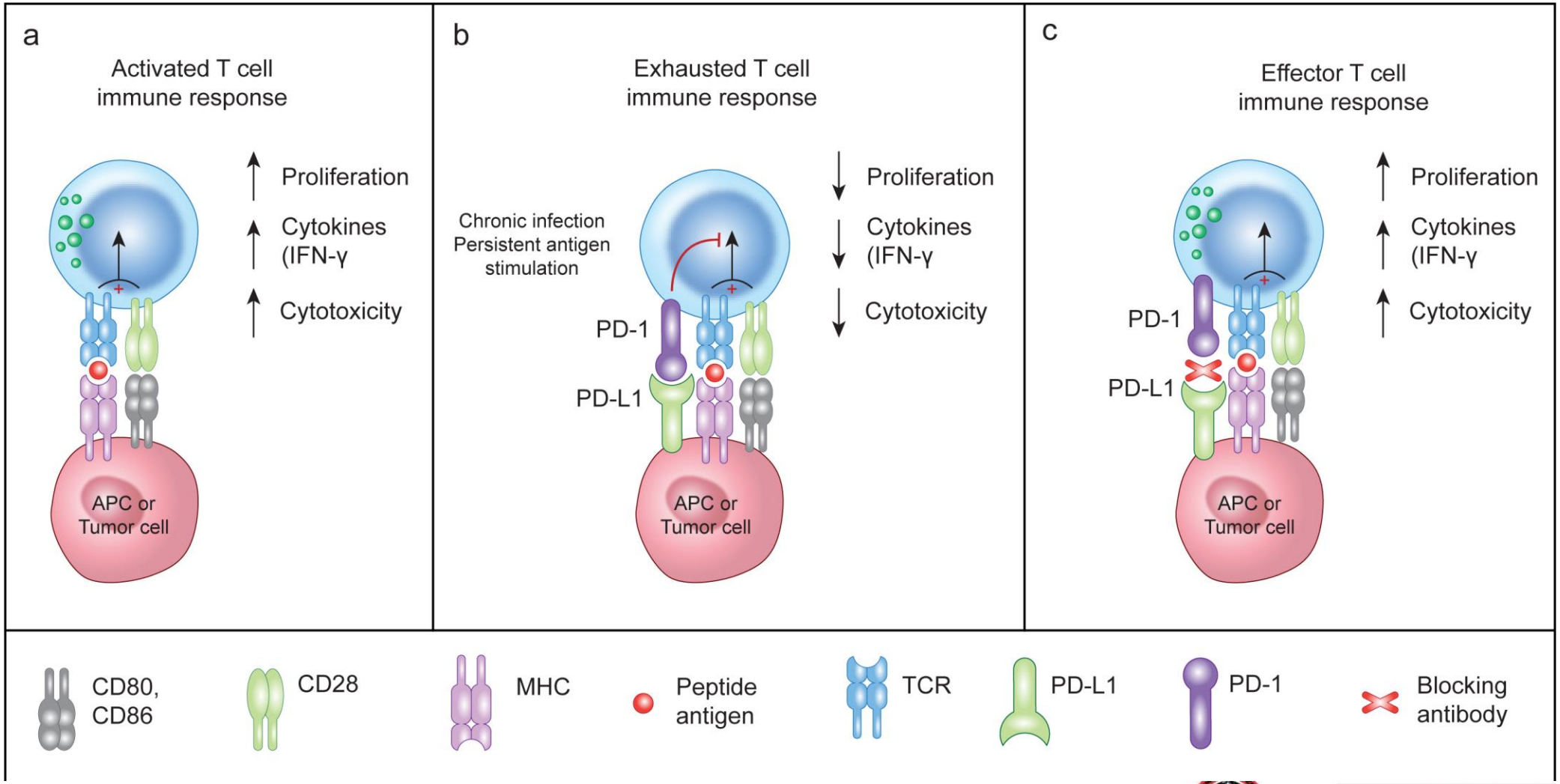
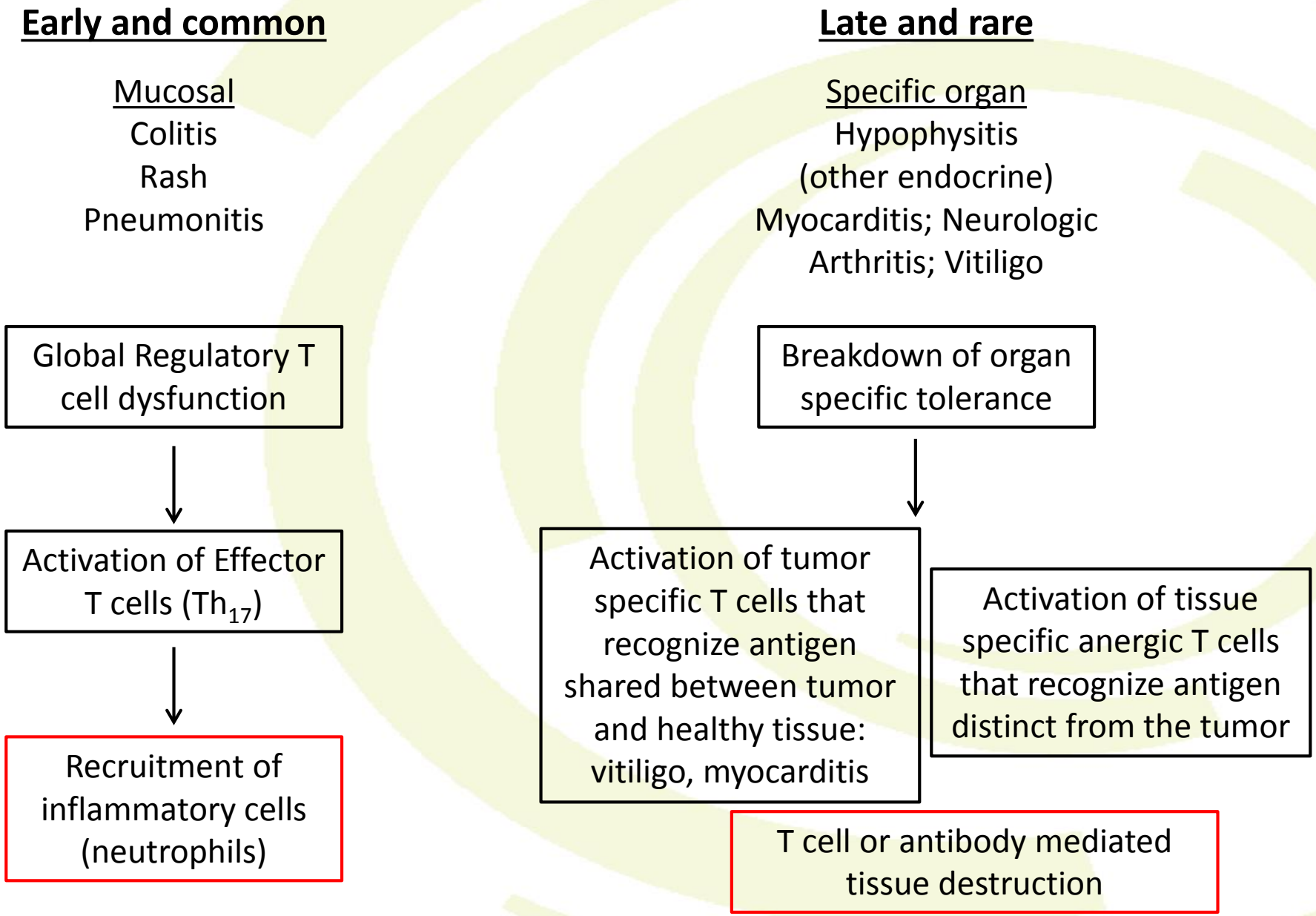
irAE Mechanism: Blocking PD-1/PD-L1 Pathway Reactivates T cells



PD-1 is the receptor on T cells – its ligand PD-L1 is on immune cells or tumor cells

Early and late irAEs may occur by distinct mechanisms



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Case Study Continued: What happened next?

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

How would you manage this patient?

(Attendees: Respond via the poll question)

a. Continue nivolumab and start steroid treatment.
b. Continue nivolumab and start broad-spectrum antibiotics.
c. Discontinue nivolumab and start steroid treatment.
d. Discontinue nivolumab and start broad-spectrum antibiotics.

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Case Study Continued: Outcome

- 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

General principals of immunotherapy toxicity management

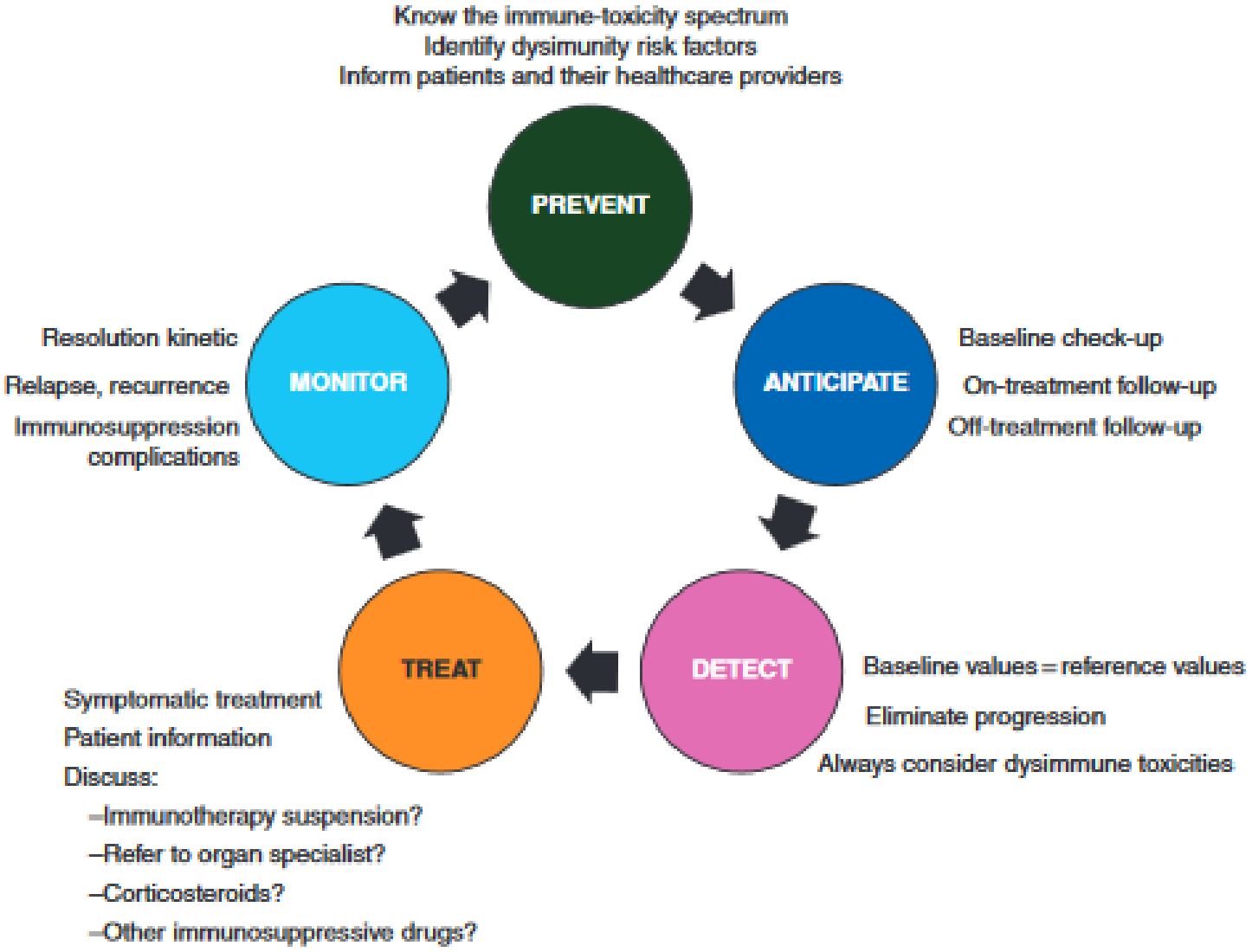

Figure 1. The five pillars of immunotherapy toxicity management.

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

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)

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

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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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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

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

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)

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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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General Corticosteroid Management Guidelines for irAE Treatment

Grade of irAE (CTCAE/equivalent)	Corticosteroid Management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

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Skin toxicity – rash/dermatitis/Pruritus

Grade	Management
1	**Rash/dermatitis**: Continue ICI; Oral antihistamines; Topical corticosteroids **Pruritus**: Emollients with cream or ointment based, fragrance-free products
2	**Rash/dermatitis:** Continue ICI; Non-urgent dermatology referral; Oral antihistamines; Topical corticosteroids **Pruritus:** Dermatology referral; Class I topical steroid; Oral corticosteroids
3	**Rash/dermatitis:** Hold ICI; Same day dermatology consult; Rule out systemic hypersensitivity; Oral antihistamines; Systemic corticosteroids; Prednisone **Pruritus:** Dermatology referral; GABA agonist (pregabalin, gabapentin 100-300 mg TID); Oral corticosteroid

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Diarrhea/ Enterocolitis

Grade	Management
1	• Close follow up within 24–48 h for changes or progression • Continue ICI • If symptoms persist, start routine stool and blood tests • Bland diet advisable during period of acute diarrhea • Anti-diarrheal medication is optional but not highly recommended when infectious work-up is negative.
2	• Hold ICI • Outpatient stool and blood work; CRP, ESR, fecal calprotectin, lactoferrin, imaging and endoscopy are optional • If diarrhea only, observe for 2–3 days. If no improvement start prednisone 1 mg/kg/day (or equivalent dose of methylprednisolone); anti-diarrheal medication is not recommended • If diarrhea and colitis symptoms (abdominal pain +/− blood in BM), start prednisone 1 mg/kg/day (or equivalent dose of methylprednisolone)immediately • If colitis returns on resuming ICI: Grade ≤ 2: temporarily hold ICI; Grade ≥ 3: permanently discontinue ICI
3 and 4	**Grade 3:** withhold ICI; consider resuming ICI when corticosteroid is tapered to ≤10 mg/day and patient remains symptom-free (grade ≤ 1). Consider hospitalization **Grade 4:** permanently discontinue ICI and hospitalize • Blood and stool infection work-up, inflammatory markers, imaging, endoscopy and GI consult • Start intravenous prednisone immediately • If refractory or no improvement on IV corticosteroid, start prednisone for 3 days • Consider other anti-inflammatory agents e.g. infliximab 5 mg/kg, which can be given again after two weeks if a second dose is needed. Vedolizumab may also be used.

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Endocrinopathies

Hypophysitis	Hypothyroidism	Hyperthyroidism	Type 1 diabetes (CTCAE defines hyperglycemia not diabetes)
• Hold ICI if ≥ grade 2 irAE until work up is completed and appropriate hormone replacement is started • If central adrenal insufficiency: start physiologic steroid replacement • If central hypothyroidism: start thyroid hormone • If central hypogonadism, repeat hormone levels in 2–3 months and consider testosterone in men or HRT in women if appropriate for cancer type *For severe/life-threatening symptoms such as adrenal crisis, severe headache, visual field deficiency:* • Hospitalize as appropriate. • High dose corticosteroid in the acute phase, followed by taper over 1 month. • Adrenal crisis should be managed per standard guidelines. • If central hypothyroidism, replace thyroid hormone after corticosteroids have been initiated	• Hold ICI for ≥grade 3 irAEs • ICI can be continued after resolution of symptoms to grade 2 or better. • Start standard thyroid replacement therapy: initial dose can be the full dose (1.6 mcg/kg) in young, healthy patients, but a reduced dose of 25 - 50mcg should be initiated in elderly patients with known cardiovascular disease. • Repeat TSH and free T4 testing after 6–8 weeks and adjust thyroid hormone dose accordingly. If TSH is above reference range, increase thyroid hormone dose by 12.5 mcg to 25 mcg • After identification of the appropriate maintenance dose, further evaluation is required every year, or sooner if patient's status changes • After identification of the appropriate maintenance dose, further evaluation is required every year, or sooner if patient's status changes	• Hold ICI for ≥ grade 3 irAEs • Standard therapy for hyperthyroidism should be followed • *Thyroiditis* is self-limiting and has 2 phases: ○ In the hyperthyroid phase, patients may benefit from beta blockers if symptomatic (e.g., atenolol 25–50 mg daily, titrate for HR < 90 if BP allows). Monitor closely with regular symptom evaluation and free T4 testing every 2 weeks. ○ Introduce thyroid hormones (see hypothyroidism management) if the patient becomes hypothyroid (low free T4/T3, even if TSH is not elevated). • *Graves' disease* should be treated per standard guidelines.	• *Type 1 DM with diabetic ketoacidosis*: Hold ICI; hospitalize and initiate treatment per standard guidelines. • *Type 1 DM without diabetic ketoacidosis*: Hold ICI for hyperglycemia ≥ grade 3. Treat with insulin and continue ICI when patient recovers to grade 1. • Treat with insulin per standard guidelines and restart ICI when patient recovers to grade 1. • Provide patient education on diet and lifestyle modification, and blood glucose testing

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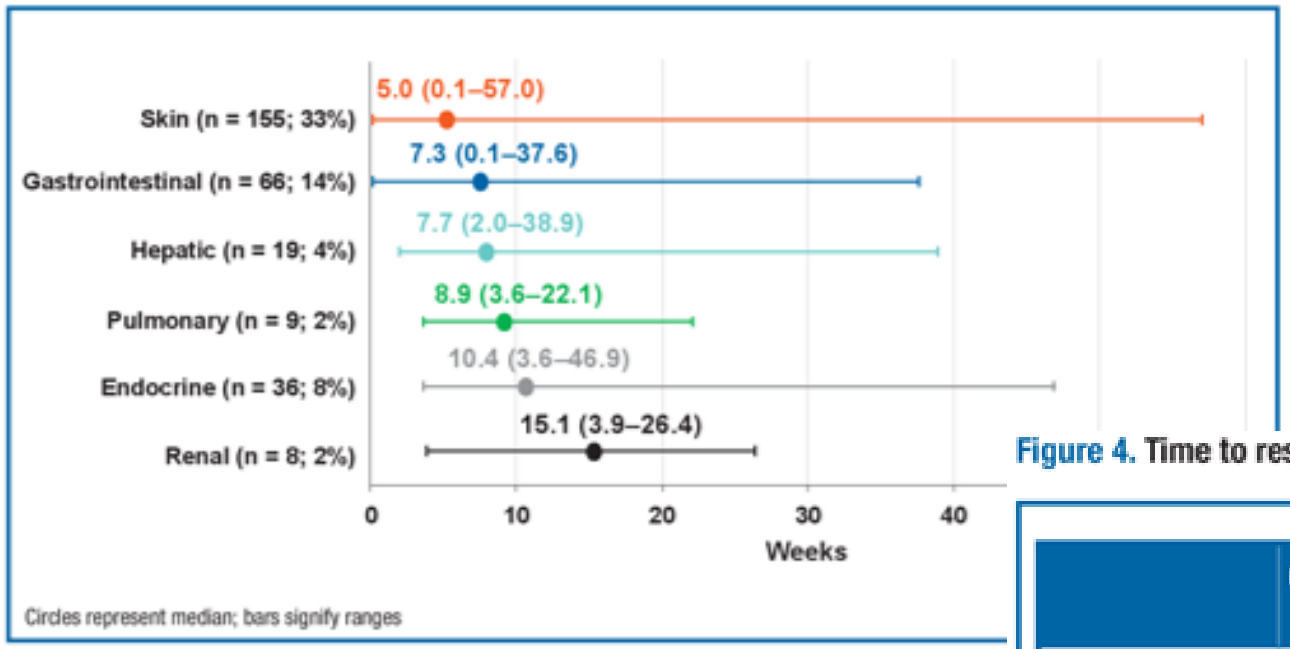
Hepatic Adverse Events

Grade of Liver Test Evaluation (NCI CTCAE v4)	Management	Follow up
Grade 1: AST or ALT > ULN to 3.0x , ULN and/or total bilirubin (T. bill) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function test (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 worse: 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 – 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 (g) twice daily (BID); if no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Time to onset and resolution of AEs with PD-1

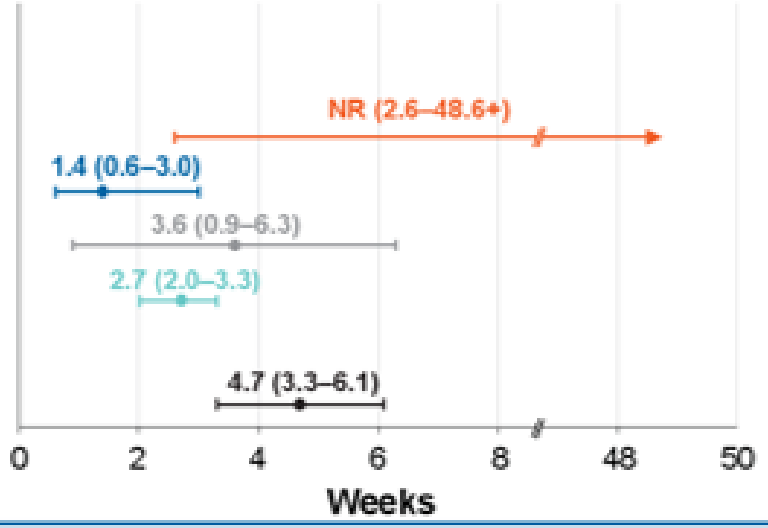
Figure 1. Time to onset of select treatment-related AEs (any grade; N = 474)



- 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