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Improving Counseling for the Cancer Patients on Immunotherapy You Don't Know You're Seeing

Faculty
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This presentation will serve as a basic overview of immunotherapy, intended for community pharmacists, in order to increase knowledge and skills between non-oncology pharmacists and patients receiving immunotherapy. The session will include a review of immunotherapy indications for use, mechanism of action and commonly experienced immune-related adverse events. While recognizing that community pharmacists will not be dispensing immunotherapy to patients, it is still critical for community pharmacists to be aware of the needs of patients receiving immunotherapy in order to create a pharmacy environment that encourages patients to share information about their cancer management, especially, when they are receiving medications from outside of the community pharmacy. Information on the management of immune-related adverse events will incorporate evidenced-based guidelines so that community pharmacists are well positioned to make recommendations/referrals for the commonly encountered immune-related adverse events. Key concepts that community pharmacists would need to know will be reinforced and applied through application-based cases in order to highlight counseling points that should be communicated to patients.

Learning Objectives

Pharmacist

1. Recognize the importance of collecting and evaluating patient data, related to cancer diagnosis and use of immunotherapy, in order to meet the needs of patients and provide quality care
2. Identify the most common/concerning immune-related adverse events in order to recognize patients who are appropriate for self-management versus immediate medical attention
3. Utilize guidelines and resources in order to recommend an evidence-based, patient-specific plan for immunotherapy-related adverse events

Pharmacy Technician

1. Recognize the importance of collecting and evaluating patient data, related to cancer diagnosis and use of immunotherapy, in order to meet the needs of patients and provide quality care
2. Identify the most common/concerning immune-related adverse events in order to recognize patients who are appropriate for self-management versus immediate medical attention
3. Utilize guidelines and resources in order to recommend an evidence-based, patient-specific plan for immunotherapy-related adverse events

Nurse

1. Recognize the importance of collecting and evaluating patient data, related to cancer diagnosis and use of immunotherapy, in order to meet the needs of patients and provide quality care
2. Identify the most common/concerning immune-related adverse events in order to recognize patients who are appropriate for self-management versus immediate medical attention
3. Utilize guidelines and resources in order to recommend an evidence-based, patient-specific plan for immunotherapy-related adverse events

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Pharmacists, Pharmacy Technicians, Nurses

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Pharmacist	Pharmacy Technician	Nurse
0798-0000-20-071-H01-P	0798-0000-20-071-H01-T	0798-0000-20-071-H01-N

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Counseling for the Cancer Patients on Immunotherapy You Don't Know You're Seeing

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

1. Recognize the importance of collecting and evaluating patient data, related to cancer diagnosis and use of immunotherapy, in order to meet the needs of patients and provide quality care

2. Identify the most common/concerning immune-related adverse events in order to recognize patients who are appropriate for self-management versus immediate medical attention

3. Utilize guidelines and resources in order to recommend an evidence-based, patient-specific plan for immunotherapy-related adverse events

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Immunotherapy and the Community Pharmacist

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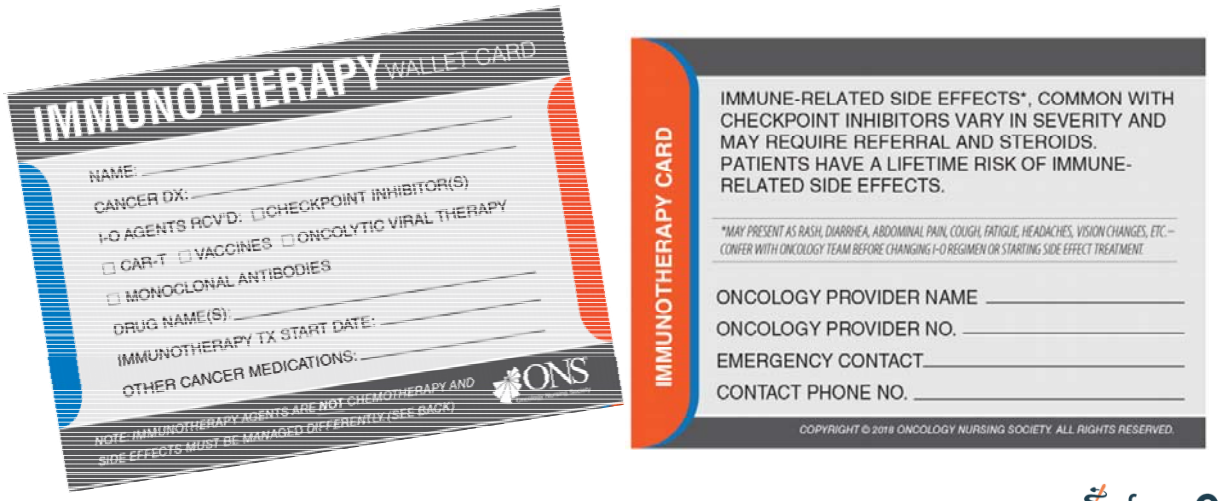
Collecting Relevant Data for Patients with Cancer



- https://www.ons.org/sites/default/files/2019-01/IO%20Card%201-sided_Vertical.pdf

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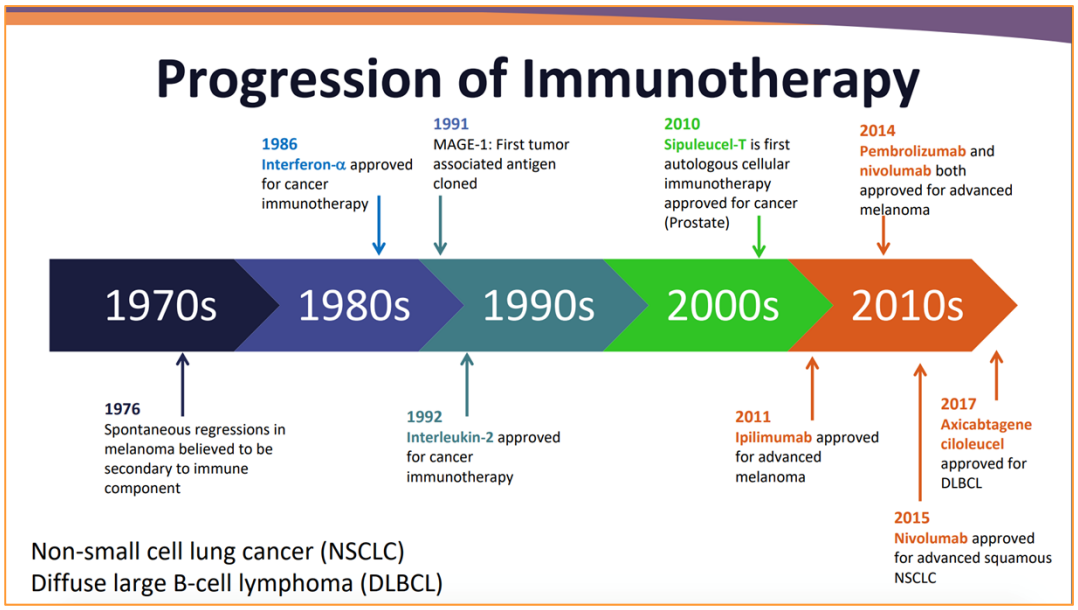
Progression of Immunotherapy



Walko CM, et al. Evolving Role of Immunotherapy in Cancer Treatment. Presented at: 2018 ASHP Midyear Clinical Meeting. December 2-6, 2018. Anaheim, California.

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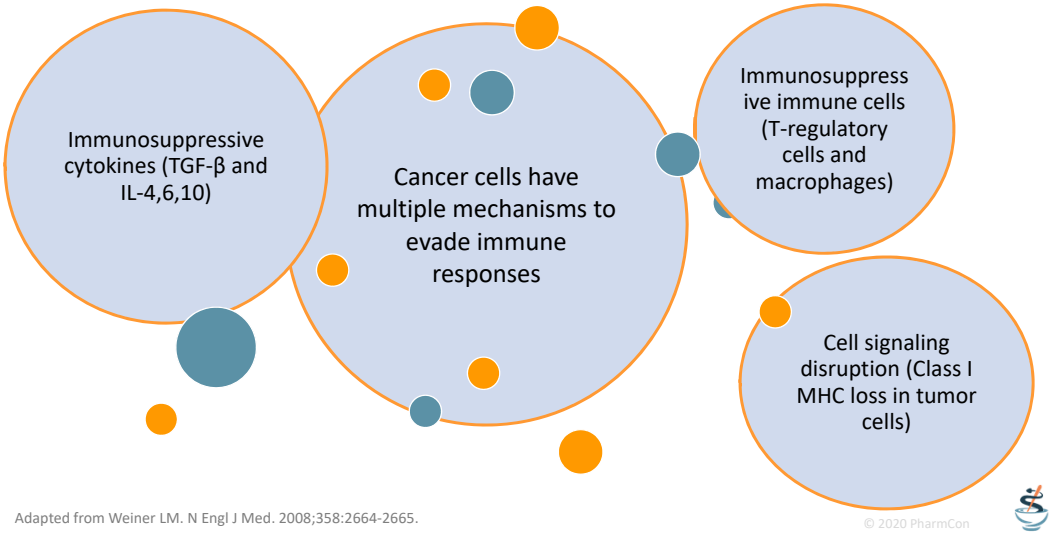
Immunotherapy Rationale



Adapted from Weiner LM. N Engl J Med. 2008;358:2664-2665.

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Immunotherapy Rationale

Based on the hypothesis that the immune system is the best tool to fight diseases

- Uses tumor specific proteins that stimulates the immune system to recognize tumor cells as foreign
- Works synergistically with other immunotherapies, traditional chemotherapy
- Avoids traditional chemotherapy toxicities
- Delivers a different way of attacking tumors

- Weiner LM. N Engl J Med. 2008;358:2664-2665.

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Basic Concepts for Immune Checkpoints

- Immune checkpoints are critical pathways for maintaining self-tolerance and preventing the immune system (T-cells) from attacking cells unsystematically
- These are considered to be the “brakes” on the immune system
- These “brakes” are used by the immune system to increase or decrease immune responses to maintain the appropriate level of immune activity

- Weiner LM. N Engl J Med. 2008;358:2664-2665.

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Immune Checkpoint Inhibitors:

Mechanisms of Action

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Immune Checkpoint Inhibitors: Indications include Solid Tumors, Lymphomas

Atezolizumab (Tecentriq™)	**PD-L1 Inhibitor**	**Human *mAB that binds to PD-L1 and blocks interaction with PD-1 and B7.1 receptors**
Avelumab (Bavencio™)		
Durvalumab (Imfinzi™)		
Cemiplimab (Libtayo™)	**PD-1 Inhibitor**	**Human *mAB that binds to PD-1 receptor and blocks interaction with its ligands PD-L1/PD-L2**
Nivolumab (Opdivo™)		
Pembrolizumab (Keytruda™)		
Ipilumumab (Yervoy™)	**CTLA-4 Inhibitors**	**Human *mAB that binds CTLA-4 receptor and blocks interaction with CTLA-4 and its ligands**

- *monoclonal antibody

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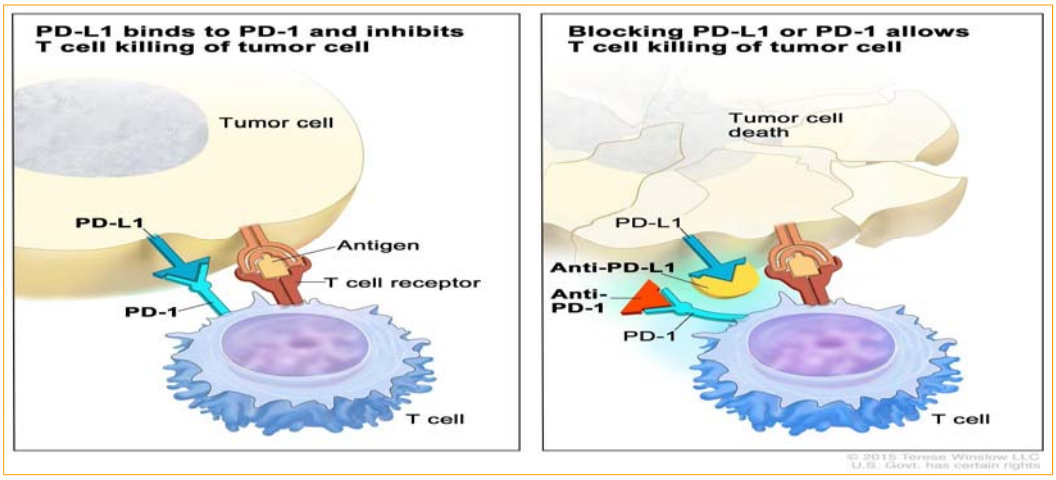
Immune Checkpoint Inhibitors: Mechanism of Action



- Credit: National Cancer Institute

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PD-L1 Immune Checkpoint Inhibitors

Drugs	Dosing	Some Approved Indications	Renal Adjustment (prior to treatment)	Hepatic Adjustment (prior to treatment)
Atezolizumab (Tecentriq™)	840 mg on days 1 and 15 every 4 week 1200 mg every 3 weeks	Breast cancer Lung cancer Bladder cancer	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Avelumab (Bavencio™)	800 mg once every 2 weeks	Renal cancer Bladder cancer Merkel cell cancer	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

- Bavencio (avelumab) [package insert]. Rockland, MA: EMD Serono, Inc.; 2020
- Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech, Inc.; 2020

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PD-1 Immune Checkpoint Inhibitors

Drugs	Dosing	Some Approved Indications	Renal Adjustment (prior to treatment)	Hepatic Adjustment (prior to treatment)
Nivolumab (Opdivo™)	240 mg every 2 weeks or 480 mg IV every 4 weeks	Skin cancer Lymphomas Lung cancer	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Pembrolizumab (Keytruda™)	200 mg every 3 weeks or 400 mg IV every 6 weeks	Lung cancer Lymphoma Bladder cancer	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

- Opdivo (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020
- Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co. Inc.; 2020

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CTLA-4 Immune Checkpoint Inhibitors

Drugs	Dosing	Some Approved Indications	Renal Adjustment (prior to treatment)	Hepatic Adjustment (prior to treatment)
Ipilumumab (Yervoy™)	3 mg/kg every 3 weeks	Skin cancer Renal cancer Colon cancer	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

- Yervoy (ipilimumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020

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Clinical Case #1

HF is a 76-year-old male with advanced stage non-small cell lung cancer (metastasis to the right adrenal gland). There are no targetable mutations and his treatment plan consists of Pembrolizumab (Keytruda™) monotherapy. What can HF expect from this immunotherapy?

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Immune Checkpoint Inhibitors versus Traditional Chemotherapy

Differences in treatment response

- Immunotherapy utilizes T cells…responses are durable

Differences in toxicity

- Traditional chemotherapy attacks rapidly dividing cells (bone marrow, hair, gastrointestinal tract)

- Immunotherapy related toxicity occurs through an autoimmune inflammatory process

- Weiner LM. N Engl J Med. 2008;358:2664-2665.

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Highlighted Immune Checkpoint Inhibitor Toxicities

Dermatologic

- Rash, pruritus, vitiligo, severe cutaneous adverse reactions (SCAR)

Gastrointestinal

- Colitis, diarrhea, pancreatitis, hepatitis

Respiratory

- Pneumonitis, pleuritis

Endocrine

- Hyper- and hypothyroidism, adrenal insufficiency, diabetes mellitus

- Brahmer JR, et al. American Society of Clinical Oncology clinical practice Guideline. J Clin Oncol 2018; 36: 1714-1768.

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National Cancer Institute: Common Terminology Criteria for Adverse Events (V.5)

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom	Mild; asymptomatic or mild symptoms; intervention may not be needed	Moderate; Minimal, local or noninvasive intervention indicated; limiting *IADL	Severe or medically significant but not immediately life-threatening; hospitalization indicated; limiting self-care **ADL	Life-threatening consequences; urgent intervention indicated	Death related to symptoms

*Instrumental Activities of Daily Living (e.g. grocery shopping, managing finances)
**Activities of Daily Living (e.g. bathing, taking medications, toileting, grooming)

- Common Terminology Criteria for Adverse Effects, Version 5. National Cancer Institute. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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Returning to Clinical Case #1

HF comes to your neighborhood pharmacy to pick up refills for blood pressure and cholesterol medications. HF complains of moderate pruritus/itching and reports of a new rash on his chest and stomach. He asks you if this could be related to his new cancer treatment and asks what can he take to relieve symptoms since it's affecting his ability to sleep and run errands (e.g. grocery shopping, prescriptions

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Dermatologic Immunotherapy-Related Adverse Events: Questions to Ask Patients

- When did you first notice the rash? Have you experienced any oozing, mouth sores or fever?
- Have there been any changes in your use of soaps, detergents, perfumes/colognes? Have you ever experienced anything like this in the past?
- Have you already tried anything to treat the rash? Has anything that you have tried made it better or worse?
- Has the rash interfered with daily activities (bathing, dressing, errands)?

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Dermatologic Immunotherapy-Related Adverse Events

- Prevalence: Cutaneous toxicities are reported in 30% to 50% of patients
  - CTLA-4 Inhibitors: 37-70%
  - PD-L1/PD-1 Inhibitors: 17-37%
- Potential adverse events:
  - Rash
  - Pruritus
  - Vitiligo
  - Bullous Dermatosis
  - Severe cutaneous adverse reactions (SCARs)

- Sibaud V. Dermatologic Reactions to Immune Checkpoint Inhibitors. Am J Clin Dermatol (2018) 19: 345.
- Brahmer JR, et al. American Society of Clinical Oncology clinical practice Guideline. J Clin Oncol 2018; 36: 1714-1768.

22

Common Terminology Criteria for Adverse Events: Pruritus

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pruritus	Mild or localized	Widespread and intermittent Skin changes from scratching (e.g. edema, papulation, oozing)	Widespread and constant Limiting self-care, sleep or *ADL	N/A	N/A
Management	Topical intervention indicated	Oral intervention indicated (e.g. anti-pruritics)	Oral corticosteroid / immunosuppressive therapy indicated	N/A	N/A

*Activities of Daily living (e.g. bathing, taking medications, toileting, grooming)

- Common Terminology Criteria for Adverse Effects, Version 5. National Cancer Institute. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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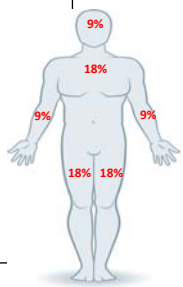
Common Terminology Criteria for Adverse Events: Rash

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash	Covers < 10% body surface area (BSA) Asymptomatic or with symptoms (e.g. burning, pruritus)	Covers 10-30% BSA with/without symptoms Limiting *IADL	Covers > 30% body surface area with moderate to severe symptoms that limit **ADL	N/A	N/A



*Instrumental activities of Daily Living (e.g. grocery, finance)
**Activities of Daily Living (e.g. bathing, taking medications, toileting, grooming)

- Common Terminology Criteria for Adverse Effects, Version 5. National Cancer Institute. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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Common Terminology Criteria for Adverse Events: Treatment Options for Rash

Grade	Treatment Options
Grade 1	Topical or oral antipruritic agents. Topical emollients and/or mild/moderate potency topical corticosteroid. Avoid irritants and sun exposure.
Grade 2	Consider withholding immunotherapy. Consider oral prednisone 0.5-1 mg/kg daily tapering over at 4-6 weeks. Topical emollients and/or moderate/high potency topical corticosteroid.
Grade 3 or 4	Withhold immunotherapy, consult Dermatology. Hospitalization needed; Initiate Methylprednisolone 1-2 mg/kg IV daily, slow taper over at 4-6 weeks when toxicity resolves.

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities.
- Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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Treatment of Immunotherapy-Related Adverse Events

Comprehensive guidelines are currently available to assist with the management of immunotherapy related adverse events:

- American Society of Clinical Oncology (ASCO)
- National Comprehensive Cancer Network (NCCN)
- Society for Immunotherapy for Cancer (SITC)

- Puzanov I, et al. J Immunother Cancer. 2017; 5(1): 95.
- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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Returning to Clinical Case of HF

Case discussion and considerations regarding HF's dermatologic symptoms

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Immunotherapy-Related Adverse Events: Corticosteroid Treatment Considerations

- Proton Pump Inhibitors may be utilized for patients at risk for gastritis
- Pneumocystis pneumonia prophylaxis varies according to institutionalized standards, but antibacterial therapy can be considered for ≥ 20 mg prednisone for ≥ 12 weeks
- Fungal prophylaxis varies according to institutionalized standards, but antifungal therapy can be considered for ≥ 20 mg prednisone for ≥ 12 weeks
- Other considerations depends of patient's risk factors: hyperglycemia, bone health (e.g. calcium/vitamin D supplementation), herpes zoster reactivation

• Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.

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Dermatologic Immunotherapy-Related Adverse Events: Which Patients Should a Community Pharmacist Refer?

- Any patient who presents with a severe cutaneous adverse reaction or Stevens-Johnson Syndrome should seek immediate care at the emergency department
- All patients with dermatologic toxicity should be referred to their medical oncologist for full and complete evaluation
- Difficult to diagnose dermatologic toxicity in a community pharmacy without the guidance of a dermatologist

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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Clinical Case #2

You notice a woman (SR) in line at the register who would like to purchase a box of loperamide (Imodium™) and she signals that she would like a consultation. You learn that SR has metastatic melanoma and began treatment with ipilumumab (Yervoy™) and nivolumab (Opdivo™) 6 weeks ago. SR complains of diarrhea (4x daily) and asks about medicine for symptoms.

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Gastrointestinal Immunotherapy-Related Adverse Events: Questions to Ask Patients

- When did you first start to have symptoms? Have you experienced any abdominal pain, stomach cramping, blood in your stool?
- Have you ever experienced anything like this in the past? Have you been diagnosed with any gastrointestinal conditions?
- Have you already tried anything to treat the symptoms? Has anything that you have tried made it better or worse?
- Have you started any new medications or antibiotics? Has the rash interfered with daily activities (bathing, dressing, errands)?

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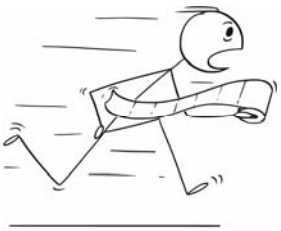
Gastrointestinal Immunotherapy-Related Adverse Events

Prevalence: Highest in patients receiving anti–CTLA-4 and anti–PD-1 combination therapy

- Colitis: 8-27%
- Diarrhea: 54%
- Hepatitis: 2-30%



Symptoms may coexist with mucous in the stools, abdominal pain, fever, rectal bleeding

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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Common Terminology Criteria for Adverse Events: Diarrhea

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting IADL*	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting ADL**	Life-threatening consequences; urgent intervention indicated	Death

*Instrumental Activities of Daily Living (e.g. grocery shopping, managing finances)
**Activities of Daily Living (e.g. bathing, taking medications, toileting, grooming)

- Common Terminology Criteria for Adverse Effects, Version 5. National Cancer Institute. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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Common Terminology Criteria for Adverse Events: Colitis

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Colitis	Asymptomatic; Clinical or diagnostic observations only; intervention not needed	Abdominal pain; mucus or blood in the stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent operative intervention	Death

- Common Terminology Criteria for Adverse Effects, Version 5. National Cancer Institute. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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Gastrointestinal Immunotherapy-Related Adverse Events: Treatment Options for Diarrhea

	Grade 2	Grade 3-4
Determine Severity	Grade 2	Grade 3-4
Initial Management	• Hold Immunotherapy until Grade 1 Symptoms • Beta-blocker for symptom relief • Consider Endocrine Consult • Consider methimazole (Graves Disease)	• Hold immunotherapy until resolution • Beta-blocker; Endocrine Consult • Hospitalize for severe cases; start 1-2 mg/kg/day methylprednisolone
Ongoing Symptoms	Treat as grade 3-4	

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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Returning to Clinical Case of SR

Case discussion and considerations regarding SR's gastrointestinal symptoms

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Gastrointestinal Immunotherapy-Related Adverse Events: Which Patients Should a Community Pharmacist Refer?

- All patients with gastrointestinal toxicity should be referred
  - Mild symptoms – refer to oncologist
  - Moderate-severe symptoms – urgent attention warranted
- Difficult to diagnose gastrointestinal toxicity in a community pharmacy so many times, further work-up is needed
- Anti-diarrheal like loperamide are best reserved for mild diarrhea
- Hydration and electrolyte replenishment are important for all patients with mild, moderate and severe colitis

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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Clinical Case #3

On a Thursday morning in your pharmacy, you hear ongoing coughing from the cold/flu aisle. You walk towards the customer and he says, “I’m coming down with something and would like some cough medicine.” You learn that WQ has metastatic adenocarcinoma of the lung and is receiving Pembrolizumab (Keytruda™) which started several weeks ago. He also has COPD and uses inhalers daily. He asks your recommendation for medications to treat his symptoms since he desperately needs relief.

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Respiratory Immunotherapy-Related Adverse Events: Questions to Ask Patients

- When did you first start to have symptoms/cough? Have you experienced any chest pain or fevers?
- Have you been diagnosed with any respiratory conditions (e.g. COPD)? Have you ever experienced a blood clot?
- Have you already tried anything to treat the symptoms? Have you ever used oxygen to help you breathe while at home?
- Have you been around any sick contacts? Have these symptoms interfered with daily activities (bathing, dressing, errands)?

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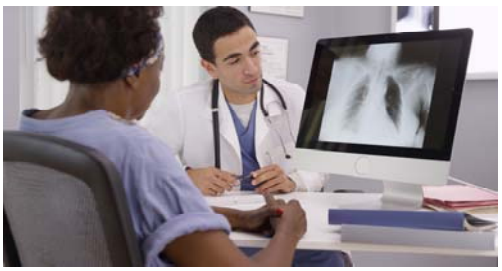
Respiratory Immunotherapy-Related Adverse Events

Immunotherapy -related pneumonitis is uncommon but is considered a potentially serious toxicity

Prevalence:
- 0-10% (~2.7%)
- Higher rates in persons with lung cancer



Characterized symptoms:
- Shortness of breath/wheezing
- Cough
- Chest pain
- Fatigue/reduced exercise tolerance

- Brahmer JR et al. J Clin Oncol. 2018; 36(17):1714-68

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Common Terminology Criteria for Adverse Events: Pneumonitis

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis	Asymptomatic; Clinical or diagnostic observations only; intervention not needed	Symptomatic; medical intervention indicated; limiting *IADL	Severe symptoms; limiting self-care **ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g. intubation)	Death

*Instrumental Activities of Daily Living (e.g. grocery shopping, managing finances)
**Activities of Daily Living (e.g. bathing, taking medications, toileting, grooming)

- Common Terminology Criteria for Adverse Effects, Version 5. National Cancer Institute. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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Common Terminology Criteria for Adverse Events: Cough

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cough	Mild symptoms; Non-prescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting *IADL	Severe symptoms; limiting self-care **ADL	N/A	N/A

*Instrumental Activities of Daily Living (e.g. grocery shopping, managing finances)
**Activities of Daily Living (e.g. bathing, taking medications, toileting, grooming)

- Common Terminology Criteria for Adverse Effects, Version 5. National Cancer Institute. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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Respiratory Immunotherapy-Related Adverse Events: Treatment Options for Pneumonitis

	Grade 2	Grade 3-4
Determine Severity	Grade 2	Grade 3-4
Initial Management	• Hold immunotherapy until Grade 1 • Prednisone 1-2 mg/kg/day, taper • Consider bronchoscopy and antimicrobials	• Discontinue immunotherapy; Hospitalization • Bronchoscopy and antimicrobials; Consult Pulmonary and Infectious Disease Specialists • Methylprednisolone 1-2 mg/kg/day
Ongoing Symptoms	Treat as grade 3-4	Alternative immunosuppressive therapy: infliximab, mycophenolate or IVIG

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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Returning to Clinical Case of WQ

Case discussion and considerations regarding WQ's respiratory symptoms

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Respiratory Immunotherapy-Related Adverse Effects: Who Should a Community Pharmacist Refer?

- Respiratory symptoms can quickly progress so all patients should be referred to their oncologist imaging and further work-up
- Patients with severe or rapidly progressing respiratory symptoms should be referred to urgent care or the Emergency Department
- Cough suppressants or rescue inhalers should not be used in place of contacting the medical oncologist for further work-up or seeking urgent care

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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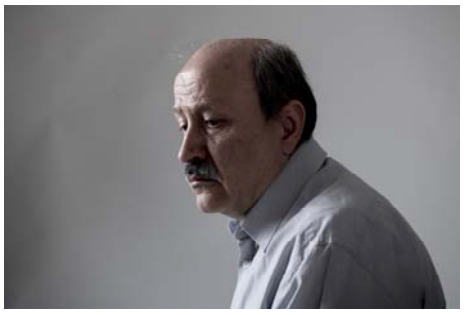
Clinical Case #4

AL is a 68-year-old male with a past medical history of diabetes type II. He was diagnosed with metastatic bladder cancer and started on Atezolizumab (Tecentriq™). He comes to the pharmacy reporting his FITBIT shows a resting heart rate of 93 (baseline 65). He reports fatigue and called out to work twice each week for the past month. He asks for a supplement to boost his energy as he looks in his bag to show you his laboratory findings.



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Endocrine Immunotherapy-Related Adverse Effects: Questions to Ask Patients

- When did you first start to have symptoms of fatigue? Have you experienced any changes in your diet or noticed changes in your blood sugars?
- Have you been diagnosed with any new medical conditions?
- Have you already tried anything to treat the symptoms? Has anything made your symptoms better or worse?
- Have these symptoms interfered with daily activities (bathing, dressing, errands)?

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Endocrine Immunotherapy-Related Adverse Events

Prevalence:

- ~10%

Most common endocrine-related events:

- Thyroid dysfunction
- Diabetes Mellitus
- Adrenal gland dysfunction

Laboratory measurements:

- Thyroid stimulating hormone, Free Thyroxine-4, Adrenocorticotropic hormone, cortisol, Follicle stimulating hormone, Luteinizing hormone

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

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Common Terminology Criteria for Adverse Events: Hyperthyroidism

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperthyroidism	Asymptomatic or mild symptoms (e.g. symptoms include sweating, fatigue, heat intolerance, abnormal heart rhythm/rate)	Moderate symptoms, able to perform *ADL	Severe symptoms, medically significant or life-threatening consequences, unable to perform *ADL		Death

*Activities of Daily Living (e.g. bathing, taking medications, toileting, grooming)

- Common Terminology Criteria for Adverse Effects, Version 5. National Cancer Institute. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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Endocrine Immunotherapy-Related Adverse Events: Treatment Options for Hyperthyroidism

	Grade 2	Grade 3-4
Determine Severity	Grade 2	Grade 3-4
Initial Management	• Hold immunotherapy until Grade 1 symptoms • Beta-blocker for symptom relief • Consider Endocrine Consult • Consider methimazole (Graves disease)	• Hold immunotherapy until resolution • Beta-blocker; Endocrine Consult • Hospitalize for severe cases; start1-2 mg/kg/day methylprednisolone
Ongoing Symptoms	Treat as grade 3-4	

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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Common Terminology Criteria for Adverse Events: Hypothyroidism

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypothyroidism	TSH <10 mIU/L and asymptomatic	Moderate symptoms; able to perform ADL; TSH persistently > 10 mIU/L	Severe symptoms, medically significant or life-threatening consequences; unable to perform *ADL		Death
Management	Should continue therapy with close follow-up, monitoring of TSH, Free thyroxine-4 (FT4)	Prescribe thyroid hormone supplements in symptomatic patients or in asymptomatic patients with TSH levels that persist > 10 mIU/L	Hold immunotherapy until symptoms resolve to baseline with appropriate supplementation; Endocrine consultation; May admit for IV therapy if signs of myxedema (bradycardia, hypothermia). Thyroid supplementation and reassessment as in G2		N/A

*Activities of Daily Living (e.g. bathing, taking medications, toileting, grooming)

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- Common Terminology Criteria for Adverse Effects, Version 5. National Cancer Institute. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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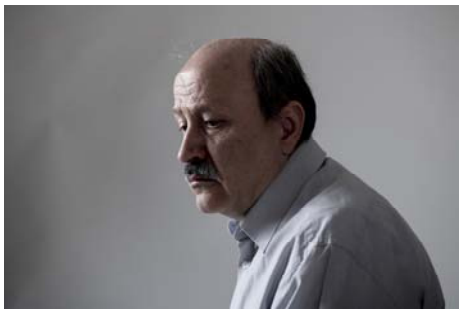
Returning to Clinical Case of AL

Case discussion and considerations regarding AL's endocrine-related symptoms



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Endocrine Immunotherapy-Related Adverse Effects: Who Should a Community Pharmacist Refer?

- All patients with potential endocrine toxicity should be referred
  - Mild symptoms – refer to oncologist
  - Moderate-severe symptoms – urgent attention warranted
- Difficult to diagnose endocrine toxicity in a community pharmacy so many times, further work-up is needed including laboratory tests
- Vitamins or supplements should not be recommended in place to further work-up

- Brahmer JR, et al. J Clin Oncol 2018; 36: 1714-1768.
- National Comprehensive Cancer Network. (2019). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

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Checkpoint Inhibitor Immunotherapy Use in Autoimmune Disorders

There are several dozen distinct autoimmune disorders:

- ~ 5% of the U.S. population has an autoimmune disorder
- Patients with autoimmune disorders were not included in immunotherapy clinical trials
- Checkpoint inhibitor use is based on risk versus benefit
- Single agent monotherapy has been safely administered however there is a higher risk of flare

- Weber JS et al. J Clin Oncol. 2012; 30:2691-7
- Donia M et al. Semin Immunopathol. 2017; 39:333-7
- Crowson CS et al. Arthritis Rheum. 2011; 63:633-9

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Key Takeaways

Key Takeaway #1

- Immune checkpoint inhibitors use immune modulation allowing T-cells to kill tumor cells for the treatment of both solid tumors and lymphomas

Key Takeaway #2

- Community pharmacist education is needed for early recognition of immunotherapy related adverse events in order to identify when self-treatment versus oncologist referral or urgent care is warrant

Key Takeaway #3

- Immune-related toxicities are unique and require rapid recognition. Moderate-severe treatment commonly involves corticosteroids

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Thank You

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Activity Test

Improving Counseling for the Cancer Patients on Immunotherapy You Don't Know You're Seeing

Activity tests must be completed online at www.freeCE.com.
A passing grade of 70 or higher and completion of an online activity evaluation are required to earn credit.

1. GO is a 72-year-old male who comes to your community pharmacy and inquires about moderate pruritus and rash covering his entire chest and abdomen. You suspect it is a Grade 2 macular papular rash associated with recent immunotherapy since GO has metastatic lung cancer and has been receiving Pembrolizumab (Keytruda ™). Once this is confirmed by the medical oncologist, how should GO's rash be managed?
    a. Diphenhydramine PO at bedtime
    b. Low potency topical steroid applied to affected area
    c. Loratadine PO with Prednisone PO daily
    d. Permanent pembrolizumab (Keytruda™) discontinuation

2. GO has now been started on prednisone (1 mg/kg – 80 mg by mouth daily). His initial taper was restarted due to a flare of his symptoms so a slow taper will occur over 6 weeks. Which of the following medications should be considered as part of his prednisone treatment plan?
    a. Alendronate orally weekly
    b. Fluconazole orally daily
    c. Ibuprofen orally daily
    d. Omeprazole orally daily

3. How would a pharmacist be aware that patients are on immunotherapy if the pharmacist is not dispensing that medication?
    a. Requesting access to the local hospital's Electronic Health Record
    b. Having technicians ask every patient if they are on immunotherapy
    c. Engaging the patient at prescription drop off/pick-up and during OTC purchases
    d. Reviewing claims data from insurance companies

4. Which of the following screening questions is correctly matched to a related adverse event from immunotherapy?
    a. Rash – When did you first notice the rash? Have you experienced any oozing, mouth sores or fever?
    b. Diarrhea – Have there been any changes in your use of soaps, detergents, perfumes/colognes?
    c. Endocrine – Have you been diagnosed with any respiratory conditions (e.g. COPD?)
    d. Cough – Have you experienced any changes in your diet or noticed changes in your blood sugars?

5. Checkpoint inhibitors utilize modulation of which of the following immune cells?
    a. B-lymphocytes
    b. Eosinophils
    c. Neutrophils
    d. T-cells

6. Which of the following medications is the first-line recommended treatment for moderate-severe immunotherapy-associated colitis?
    a. Infliximab
    b. Loperamide
    c. Mycophenolate
    d. Prednisone

7. Patient SC has experienced moderate Grade 2 diarrhea and colitis. Which of the following options would you expect the oncologist to recommend for SC's immunotherapy related gastrointestinal symptoms?
    a. SC should continue her current regimen with nivolumab and ipilumumab
    b. SC should temporarily withhold treatment with nivolumab and ipilumumab
    c. SC should permanently discontinue treatment nivolumab and ipilumumab
    d. SC should switch nivolumab and ipilumumab to another combination immunotherapy regimen

8. DA is a patient with severe pneumonitis caused by an immune checkpoint inhibitor for the treatment of bladder cancer. Which of the following medications is based on national guidelines for the management of severe pneumonitis caused by immune checkpoint inhibitors?
    a. Albuterol inhaled
    b. Guaifenesin/Dextromethorphan PO
    c. IVIG IV
    d. Methylprednisolone IV

9. DA has begun the appropriate treatment for severe pneumonitis is responding well to therapy (e.g. no flare of symptoms has occurred with the initial treatment taper). Over what period should DA's treatment for severe pneumonitis be tapered to prevent a flare of his respiratory symptoms?
    a. 1-2 weeks
    b. 4-6 weeks
    c. 8-10 weeks
    d. Minimum of 12 weeks

10. Which of the following medical conditions would be of significant concern due to risk of flare of disease with exposure to immune checkpoint inhibitor therapies?
    a. Allergic rhinitis
    b. Epilepsy
    c. Hypertension
    d. Rheumatoid arthritis