CE IN THE MIDDAY

Novel Therapies in the Treatment of Cancer: The Emerging Role of Immunotherapies

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Questions for faculty	Turn in question card to staff or use microphone	Expand control panel (click on orange arrow) and type in your question
Evaluation	Complete evaluation when you process CE online	Complete evaluation when you process CE online

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Christine M. Walko, Pharm.D., BCOP, FCCP

- Bristol-Myers Squibb and Merck: Honoraria received for participation in the Institute for Clinical Immuno-Oncology's Melanoma Board

Ragini R. Kudchadkar, M.D

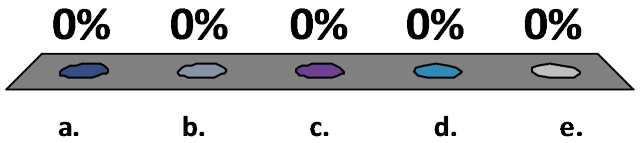
- Bristol-Myers Squibb: Advisory Board member
- Merck: Research funding received

Learning Objectives

- Discuss the current and future places in treatment for immunotherapy agents, including novel indications in both hematologic and solid tumor malignancies
- Identify common toxicities associated with immunotherapy and recommend best practices for their management
- Apply strategies for the appropriate selection of immunotherapy in patient scenarios, including consideration of biomarkers and unique patient characteristics

On average how many cancer patients being treated with immunotherapies do you provide care to each month?

a. None-I am not directly involved in patient care
b. 1-10 patients/month
c. 11-30 patients/month
d. 31-50 patients/month
e. More than 50 patients/month



Current Agents and Place in Therapy

Christine M. Walko, Pharm.D., BCOP, FCCP

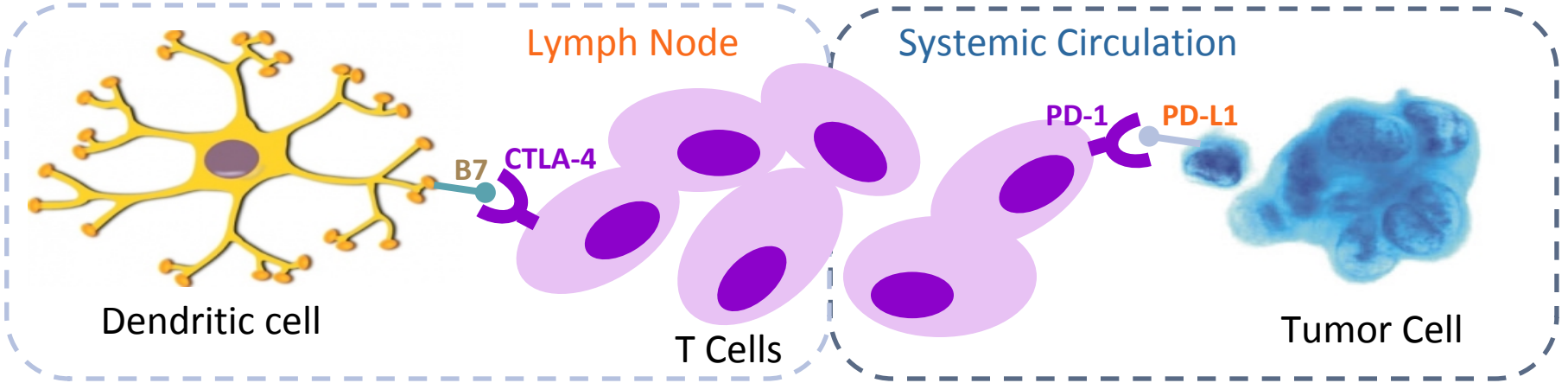
History of Immunotherapy

	Interleukin-2	Ipilimumab	Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab, Avelumab
Immune target	Nonspecific T-cell growth factor	CTLA-4	PD-1/PD-L1
Approximate number of patients with ≥ grade 3 toxicities	85%	26%	15%
Classic toxicities	Capillary leak syndrome with hypotension, fever, headache, myalgias, diarrhea, liver toxicity	Rash, diarrhea/colitis, liver toxicity, endocrine toxicity	Rash diarrhea, liver toxicity, endocrine toxicity

CTLA-4: Cytotoxic T-lymphocyte-associated antigen-4

Petrella T et al. *Cancer Treat Rev*. 2007; 33:484-96.
Horvat T et al. *J Clin Oncol*. 2015; 33:3193-8. Larkin J et al. *N Engl J Med*. 2015; 373:23-34.

CTLA-4 and PD-1 Pathways



- Ipilimumab: inhibits CTLA-4 on T-cells
- Pembrolizumab and nivolumab: inhibit PD-1 on T-cells, preventing binding to PD-L1 on tumor cells
- Atezolizumab: inhibits PD-L1 on the tumor cell
- Ultimately, prevents immune system downregulation

http://cliparts.co/animal-cell-clip-art. Ribas A. *N Engl J Med*. 2012; 366:2517-9.

Nivolumab Phase I Trial Design

N=296 patients

- Melanoma (n = 104)
- Non-small cell lung cancer (NSCLC) (n = 122)
- Renal cell carcinoma (n = 34)
- Prostate cancer (n = 17)
- Colorectal cancer (n = 19)

All patients had an ECOG performance status of ≤2 and measurable disease

BMS-936558

Phase 1 dose escalation of anti-PD-1 inhibitor

0.1 to 10 mg/kg IV every 2 weeks for up to 12 cycles or until disease progression or complete response where therapy could continue

Tumor samples analyzed for PD-L1 expression using immunohistochemistry (IHC)

- Cohorts of 3-6 patients enrolled in each cohort
  - 0.1, 0.3, 1.0, 3.0, and 10 mg/kg
- Expansion groups enrolled after no maximum tolerated dose was found

ECOG=Eastern Cooperative Oncology Group

Topalian S et al. *N Engl J Med*. 2012; 366:2443-54.

Summary of Results

- Antitumor activity was seen at all dose levels
- Objective response rate (complete or partial)
  - 28% in melanoma
  - 27% in renal cell carcinoma
  - 18% in NSCLC
- 65% of the responses were durable for 1 year or more in patients with >1 year follow up
- IHC staining for PD-1L predicted response rate
  - 0 of 17 responses in PD-1L negative tumors
  - 9 of 25 responses in PD-1L positive tumors

Topalian S et al. *N Engl J Med*. 2012; 366:2443-54.

FDA-Approved PD-1 and PD-L1 Inhibitors

	PD-1 Inhibitors		PD-L1 Inhibitors		
	Nivolumab	**Pembrolizumab**	**Atezolizumab**	**Durvalumab**	**Avelumab**
Classical Hodgkin Lymphoma	X	X			
Head and neck cancer	X	X			
Hepatocellular carcinoma	X				
Gastric cancer		X			
Melanoma	X	X			
Merkel cell carcinoma					X
MSI-high colon cancer	X				
MSI-high cancers		X			
Non-small cell lung cancer	X	X	X		
Renal cell carcinoma	X				
Urothelial carcinoma	X	X	X	X	X

MSI: Microsatellite Instability

Slide updated as of 10/4/2017

Evolution of Immunotherapy

- Novel indications
  - Solid tumors with microsatellite instability
  - Rare malignancies, such as Merkel cell carcinoma and hepatocellular carcinoma
  - Hematologic malignancies, such as classic Hodgkin Lymphoma
- Combination with chemotherapy
  - Pembrolizumab in combination with pemetrexed and carboplatin for first-line treatment of non-squamous NSCLC
- Moving up into the adjuvant setting (currently both off-label)
  - Nivolumab in adjuvant melanoma
  - Durvalumab in Stage III adjuvant NSCLC

NSCLC: Non-small cell lung cancer

Case Presentation 1: TB

- TB is a 51-year-old male with metastatic colorectal cancer diagnosed 4 years ago
- He presents to your institution for a second opinion after progressing on standard therapy with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and fluorouracil, leucovorin, irinotecan (FOLFIRI) with bevacizumab.
- Review of his recent pathology from a liver biopsy showed adenocarcinoma consistent with primary colon cancer
  - Testing for DNA mismatch repair (MMR) showed the tumor has microsatellite instability **HIGH**
- **How should this patient be treated?**

Microsatellite Instability (MSI)

- DNA mismatch repair (MMR) enzymes correct errors that occur during normal DNA replication
- Inactivation of these MMR enzymes result in more errors occurring and the development of microsatellite fragments
  - Inactivation of MLH1, MSH2, MSH6, and/or PMS2
  - Can be germline or somatic (just occurring in the tumor)
- Frequency in solid tumors:
  - Colorectal cancer: 15%
  - Endometrial cancer: 22-33%
  - Other tumors: 5% or less
- **Correlated with increased number of mutations**

Keytruda (pembrolizumab) prescribing information, 2017 Sep., Gatalica Z et al. *Fam Cancer.* 2016; 15:405-12.

Mutation Load and Immunotherapy

Number of Mutations

- Improved **overall survival** with CTLA-4-inhibitors in melanoma patients with >100 mutations (p=0.04)
  - 64 patients treated with ipilimumab or tremelimumab
  - Neoantigen response signature developed
- Improved **median progression free survival (mPFS)** in lung cancer patients treated with pembrolizumab with high mutation burden
  - Patients with durable responses had a median of 302 mutations vs. 148 in those without a durable response (p=0.02)

Microsatellite Instability

- 41 patients with MMR-deficient colorectal cancer, 9 patients with other MMR-deficient cancer, and 21 MMR-intact colorectal cancer patients
  - All treated with pembrolizumab
- Whole exome sequencing mean number of somatic mutations per tumor
  - MMR-deficient: 1782 mutations
  - MMR-intact: 73 mutations
  - Higher somatic tumor burden = improved mPFS

Snyder A et al. *N Engl J Med*. 2014; 371:2189-99.

Rizvi NA et al. *Science*. 2015; 348:124-8.

Le DT et al. *N Engl J Med*. 2015; 372:2509-20

Mutation Load and Immunotherapy

- **Exciting therapy, but not everyone has a response**
  - Durable responses to anti-PD-1 therapy were seen in:
    - 31-44% of melanoma patients
    - 19-20% of lung cancer patients
    - 22-25% of renal cell carcinoma patients
  - Potential biomarkers:
    - Density of CD8+ T cells in tumors
    - Expression of PD-L1 on tumors
    - **Mutation burden and microsatellite instability (MSI):** now being reported by some molecular testing companies for individual patients

Example: MSI: Stable
Mutation Burden: **High**, 25 mutations per megabase

Topalian SL et al. *Nat Rev Cancer*. 2016; 16:275-87.

Current MSI-High Approvals

Pembrolizumab

- Treatment of **adult** and **pediatric** patients with unresectable or metastatic MSI-high or MMR deficient:
  - **Solid tumors following prior therapy with no satisfactory alternatives**
  - Colorectal cancer following prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan
  - Not yet established for pediatric patients with MSI-high central nervous system (CNS) tumors
- Data from 5 trials (n=149)
  - Objective response rate 39.6%
  - 11 complete responses
  - 48 partial responses

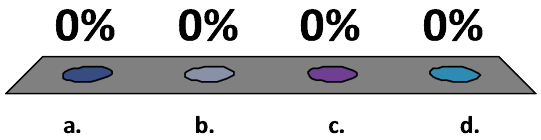
Nivolumab

- Treatment of **adult** and **pediatric** patients with unresectable or metastatic MSI-high or MMR deficient:
  - Colorectal cancer following prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan
- CheckMate 142 study (n=74)
  - Objective response 31.1%
  - Disease control for $\geq$ 12 weeks: 69%

Keytruda (pembrolizumab) prescribing information, 2017 Sep. Opdivo (nivolumab) prescribing information, 2017 Sep.
Overman MJ et al. *Lancet*. 2017; 18:1182-91.

TB has MSI-high, pretreated metastatic colorectal cancer. Which of the following is the best treatment for him at this time?

a. Durvalumab
b. Pembrolizumab
c. Atezolizumab
d. Ipilimumab



Case Presentation 2: LC

- LC is a 59-year-old female former light smoker who began experiencing persistent cough and intermittent abdominal pain
- Chest CT showed a right upper lobe (RUL) lung lesion and masses involving the liver and right adrenal gland
- Biopsy of the RUL lesion showed adenocarcinoma consistent with primary lung malignancy
  - EGFR, ALK, ROS1, BRAF, MET, and RET all negative
  - PD-L1 tumor proportion score = 75%
- **How should this patient be treated?**

CT=computerized tomography

EGFR, ALK, ROS1, BRAF, MET, and RET refer to specific gene rearrangements that have been linked to lung cancer.

$CD8^+$ Cell Infiltration in Tumors

- First immunotherapy biomarker to be explored
- Primary site of action for PD-1 inhibitors is in the tumor
  - $CD8^+$ killer T-cells identify and bind to a target
  - $CD8^+$ cytotoxic T-cell density at the invasive tumor edge correlated with response to PD-1 inhibitors in melanoma
  - No T-cell related biomarker has been sufficiently robust and validated yet

Topalian SL et al. *Nat Rev Cancer*. 2016; 16:275-87.

PD-L1 Biomarker Diagnostic Tests

Companion Diagnostic

- In vitro diagnostic device that provides information **essential** for the safe and effective use of the associated drug
- PD-L1 IHC 22C3 pharmDx in NSCLC patients receiving pembrolizumab
  - Determines a Tumor Proportion Score (TPS)
  - ≥ 50% for first-line metastatic treatment
  - ≥ 1% for treatment following progression on platinum-based therapy

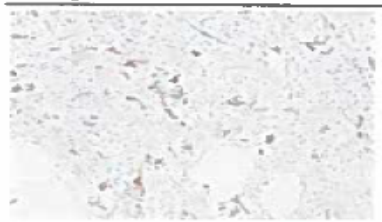
Complementary Diagnostic

- Improves the risk/benefit ratio of a specific drug but does not restrict access to the drug based on presence of the biomarker
- PD-L1 IHC 28-8 test for nivolumab in patients with melanoma and NSCLC
- VENTANA PD-L1 (SP142) Assay for atezolizumab in patients with bladder cancer and NSCLC
  - PD-L1 staining of any intensity of tumor infiltrating immune cells in ≥ 5% of the tumor area in bladder cancer is associated with increased overall response rate
  - PD-L1 membrane staining of any intensity in ≥ 50% of tumor cells or tumor infiltrating immune cells covering ≥ 10% in the NSCLC was associated with improved overall survival

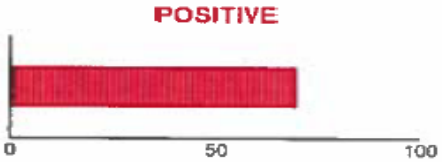
Scheerens H et al. *Clin Transl Sci*. 2017; 10:84-92.

PD-L1 22C3 pharmDx Immunohistochemistrv (IHC)

Prognostic/Predictive Markers



PD-L1 22C3 FDA (KEYTRUDA®): POSITIVE
Tumor Stained: 70%
Intensity: Moderate



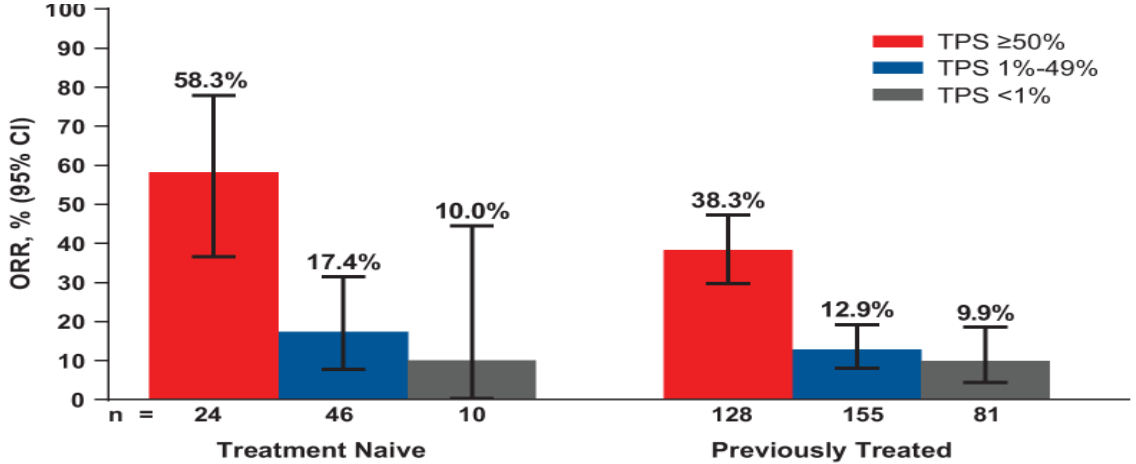
Reference Ranges	
Positive	>/=50%
Negative	<50%

Intended Use:
PD-L1 22C3 FDA (KEYTRUDA®):
PD-L1 IHC 22C3 pharmDx is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue using EnVision FLEX visualization system on Autostainer Link 48. PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab). PD-L1,22C3 pharmDx™kit (package insert). DAKO An Agilent Technologies Company, 6392 Via Real Carpinteria, CA 93013; P03951_02/SK00621-5/2015.09 p. 1-12

Methodology:
PD-L1 22C3 FDA (KEYTRUDA®):
PD-L1 staining was performed utilizing the DAKO FDA-approved PD-L1, 22C3 pharmDx™ protocol using the Dako Automated Link 48 platform. Following incubation with the primary monoclonal antibody to PD-L1 or the Negative Control Reagent (NCR), specimens were incubated with a Linker antibody specific to the host species of the primary antibody, and then were incubated with a ready-to-use visualization reagent consisting of secondary antibody molecules and horseradish peroxidase molecules coupled to a dextran polymer backbone. The enzymatic conversion of the subsequently added chromogen results in precipitation of a visible reaction product at the site of antigen. The color of the chromogenic reaction was modified by a chromogen enhancement reagent. The specimen then was counterstained and coverslipped. PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining. The specimen should be considered PD-L1 positive for KEYTRUDA® (pembrolizumab) eligibility if TPS >= 50% of the viable tumor cells exhibit membrane staining at any intensity.

Response and PD-L1 Expression: Non-Small Cell Lung Cancer (NSCLC)

- KEYNOTE-001 trial subset: NSCLC
  - 495 patients with advanced NSCLC treated with one of 3 different regimens of pembrolizumab
  - PD-L1 expression assessed in tumor samples by immunohistochemistry (IHC) and reported as a tumor proportion score (TPS)



ORR=objective response rate

Garon EB et al. *N Engl J Med*. 2015; 372:2018-28.
Hui R et al. *J Clin Oncol.* 2016; 33(suppl): Abstract 9026.

PD-L1 Expression

Benefits

- Immunohistochemical (IHC) testing is available and has correlated with response to PD-1 inhibitors in a variety of tumor types
- Response rate across tumor types:
  - PD-L1 positive tumors: 48%
  - PD-L1 negative tumors: 15%
  - Correlation with progression free and overall survival is still being assessed
- PD-L1 can be used to prioritize treatment options

Challenges

- PD-L1 expression can vary over time and between tumor sites
- PD-L1 can be located on the cell membrane (clinically relevant) or cytoplasm
- Different tests may produce different results because antibodies have different affinities and specificities
- Different specimen handling techniques may decrease sensitivity
- Unclear threshold values across tests, malignancies, and PD-1 inhibitors

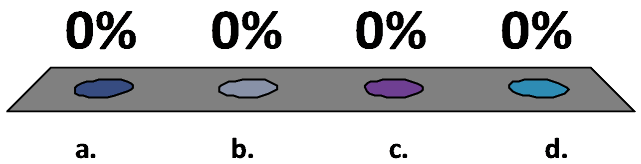
Snyder A et al. *N Engl J Med*. 2014; 371:2189-99.

Rizvi NA et al. *Science*. 2015; 348:124-8.

Topalian SL et al. *Nat Rev Cancer*. 2016; 16:275-87.

Does LC qualify for first-line pembrolizumab based on her PD-L1 TPS of 75%?

a. Yes, first-line pembrolizumab is indicated
b. No, first-line pembrolizumab is not indicated
c. Pembrolizumab is not approved for first-line therapy for NSCLC
d. Pembrolizumab is not approved for any line of therapy for NSCLC



Biomarker Future Directions

- Given the high cost and toxicity of immunotherapy agents, robust biomarkers will be helpful for optimizing therapy selection and sequencing
- Several trials have shown an association between number of somatic mutations in a tumor and response to immunotherapy
  - Ongoing trials are needed to determine threshold values
  - Differences between tumor types?
- PD-L1 expression has correlated with outcomes but responses are still seen in PD-L1 negative patients
  - Standardized assays with consistent threshold values
  - Consideration of differences between cancer types and PD-1 vs. PD-L1 inhibitors

Toxicity Management

Ragini R. Kudchadkar, M.D.

Immune-Related Adverse Events (irAEs)

Toxicity	Clinical Effects	All grades (grade 3/4)	Time Frame
Skin	Rash, vitiligo, pruritus	47-68% (0-4%)	2-3 weeks
Gastrointestinal (GI)	Diarrhea, colitis	31-46% (8-23%)	6-7 weeks
Liver	Elevated enzymes, bilirubin, hepatitis	3-9% (3-7%)	6-7 weeks
Endocrine	Hypophysitis, hypothyroidism	4-6% (1-5%)	After 9 weeks

Overall Grade 3/4:

Ipilimumab 3 mg/kg 20-30%
Ipilimumab 10 mg/kg 50%
Nivolumab or pembrolizumab 10-15%
Ipilimumab 3 mg/kg + nivolumab 1 mg/kg 50%

Weber JS et al. *J Clin Oncol.* 2012; 30:2691-7.

Phase III Nivolumab +/- Ipilimumab Toxicity

Toxicity	Nivolumab		Ipilimumab		Nivolumab and Ipilimumab	
	All grade	Grade 3 and 4	All grade	Grade 3 and 4	All grade	Grade 3 and 4
Diarrhea	**19.2**	**2.2**	**33.1**	**6.1**	**44.1**	**9.3**
Fatigue	34.2	1.3	28	1	35	4.2
Rash	25.9	0.6	32.8	1.9	40.3	4.8
Increased ALT	3.8	1.3	3.9	1.6	17.6	8.3
Increased AST	3.8	1.0	3.5	0.6	15.3	6.1
Hypothyroidism	8.6	0	4.2	0	15	0.3
Colitis	**1.3**	**0.6**	**11.6**	**8.7**	**11.8**	**7.7**
Arthralgia	7.7	0	6.1	0	10.5	0.3
Dyspnea	4.5	0.3	4.2	0	10.2	0.6

Larkin J et al. *N Engl J Med*. 2015; 373:23-34.

Case Presentation 3: RR

- RR is a 37 yo 80-kg Caucasian male who is diagnosed with Stage IV melanoma from an unknown primary site. On diagnosis, he is found to have metastatic disease of the brain and lungs
  - He begins treatment with ipilimumab 3 mg/kg and nivolumab 1 mg/kg 7/2017
  - 8/2017 he presents for his second dose and has complaints of:
    - One week ago, had one day of 6 loose stools, took loperamide with improvement
    - Currently having 3 loose stools daily, mostly after meals, taking loperamide as needed
    - Otherwise appears well, vital signs and lab work normal

Case Presentation 3: RR

(Gastrointestinal Toxicity Management)

How should this patient be managed at this time?

a. Proceed with dose 2, no new interventions
b. Delay dose 2
c. Start corticosteroids for colitis
d. Give dose of infliximab
e. Consider use of budesonide
f. Any or all of above?

Case Presentation 3: RR

(Gastrointestinal Toxicity Management)

Expert opinion

- Ipilimumab and nivolumab withheld with re-evaluation in one week
- Oral budesonide started
  - Different preparations have differences in colonic absorption (extended-release budesonide tablets [Uceris®] may be preferred over enteric-coated budesonide capsules [Entocort®])

- One week re-evaluation:
  - Patient was unable to obtain Uceris® because of health insurance restrictions
  - Still having 8-10 loose stools per day
  - Labs and vital signs are still stable

Case Presentation 3: RR (Gastrointestinal Toxicity Management)

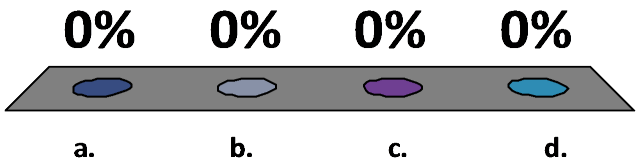
What treatment should now be considered?

a. Call in a 1 week corticosteroid taper, such as a corticosteroid dose pack

b. Hold further ipilimumab, give nivolumab. The diarrhea will resolve on its own without further intervention as long as no additional treatment is given

c. Hold further ipilimumab, treat with corticosteroids and taper over 4-6 weeks if improved. Restart ipilimumab once diarrhea is resolved

d. Discontinue ipilimumab/nivolumab. Start 1mg/kg of intravenous corticosteroids



Gastrointestinal irAEs Overview

- Inflammation can be anywhere in GI tract (mucositis and gastritis, enteritis but most commonly colitis)
- Diarrhea: requires attention
  - New and watery
  - Increased frequency >50% baseline
  - Duration
  - Bloody
- Grade 1 and 2
  - Treat symptomatically
  - Rule out other causes
  - No need for systemic corticosteroids
  - Follow closely for resolution

Gastrointestinal irAEs Overview

- Diarrhea is a frequent irAE (with ipilimumab/ nivolumab, ipilimumab, rare but occurs with nivolumab or pembrolizumab)
  - Most cases are mild or moderate
  - Biopsy demonstrates inflammatory colitis and T-cell infiltrates
  - Most cases respond to either symptomatic treatment or corticosteroids (needs 4-6 week taper)
  - Can rarely lead to GI perforation (<1%) requiring surgery
- When do you retreat?

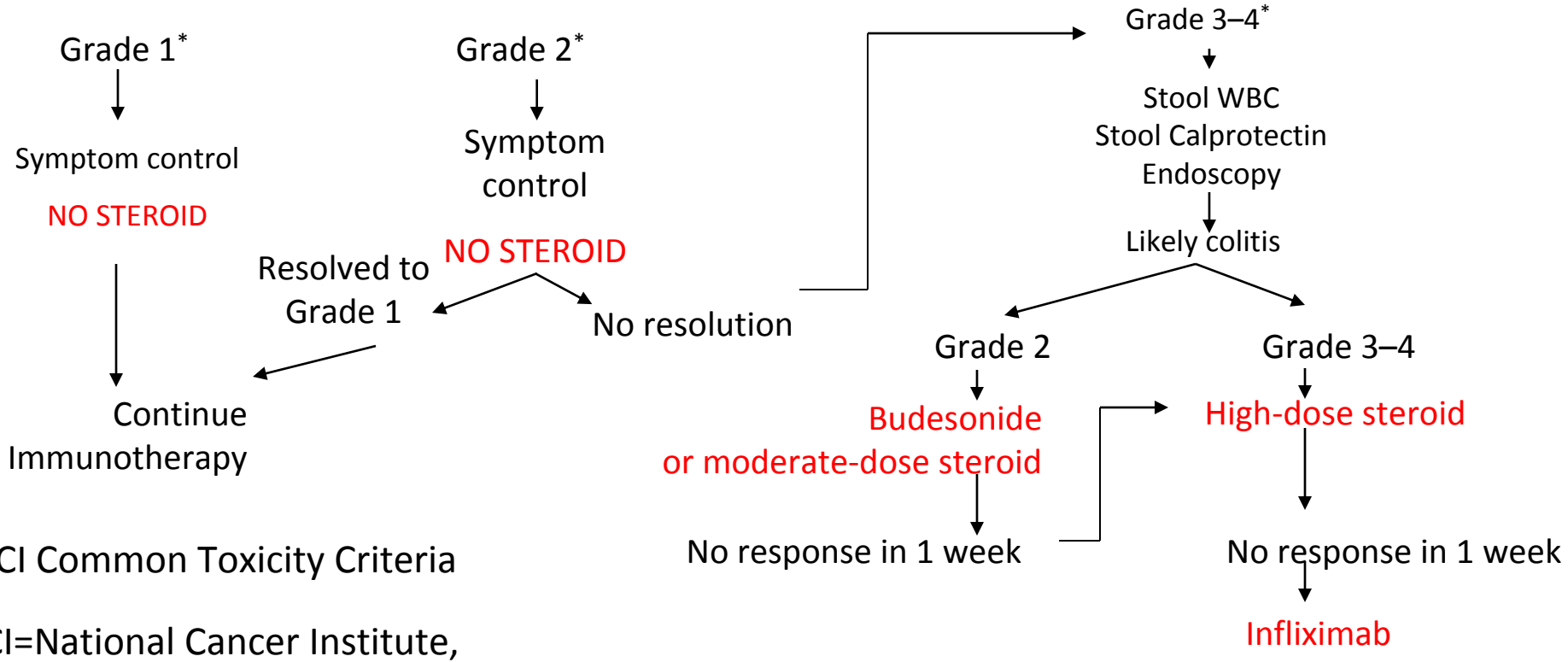
Weber JS et al. *J Clin Oncol.* 2012; 30:2691-7.

Gastrointestinal irAEs Timing

- With single-agent immunotherapy, mostly commonly seen about 6-8 weeks after start of treatment
- Can be seen after any dose of immunotherapy
- Case reports of colitis after being off immunotherapy for 3-6 months
- Timing altered by combination CTLA-4 and PD-1 blockade
- Rarely seen in patient on maintenance immunotherapy (after more than 6 doses)

Weber JS et al. *J Clin Oncol.* 2012; 30:2691-7.

Management Algorithm: Diarrhea



*NCI Common Toxicity Criteria

NCI=National Cancer Institute,
WBC=white blood cells

O'Day et al. *Cancer*. 2007; 110:2614-27.

Case Presentation 3: RR

(Gastrointestinal Toxicity Management)

- RR does well and after 1 week of oral prednisone 80 mg/day is now having formed stools and 2-3 bowel movements per day.

- How should the prednisone be tapered?

Case Presentation 3: RR

(Gastrointestinal Toxicity Management)

- RR does well until decreasing to prednisone 40mg per day.
  - He calls the clinic with increasing diarrhea at 6-8 loose stools per day

What do you do next?

a. Increase prednisone to 1mg/kg (80mg), resume taper when stools are formed.
b. Continue 40 mg of prednisone and bring him in for infliximab 5mg/kg IV
c. Increase prednisone to 60 mg/day (the lowest dosage recently associated with formed stools)

Case Presentation 3: RR

(Gastrointestinal Toxicity Management)

- RR is increased to prednisone 60mg per day and given 1 dose of infliximab with full resolution of symptoms.
  - Tapered off corticosteroids over one month
  - Scans show a partial response

How do you proceed with future treatment?

a. Complete the rest of induction therapy with ipilimumab and nivolumab?
b. Discontinue nivolumab and ipilimumab?
c. Start maintenance nivolumab at 3mg/kg?

Can you skip the corticosteroids and go straight to infliximab?

www.clinicaltrials.gov

NCT02763761

Closed early due to slow accrual

When to perform endoscopy?

- Refractory colitis
- Inconsistent patient history
- Alternative diagnosis (*C.difficile*, cytomegalovirus, radiation) under consideration

Beck KE. et al. *J Clin Oncol*. 2006; 24:2283-9.

Case Presentation 4: LM

(Skin Toxicity Management)

- LM is a 33 yo female who is currently receiving adjuvant nivolumab on trial for resected stage III melanoma
- At her one month visit, she reports pruritus without evidence of rash
  - Do you continue with the next cycle?
  - Recommendation considerations?
    - Antihistamines, moisturizers, avoid hot showers

Case Presentation 4: LM (Skin Toxicity Management)

LM calls the clinic after 3 doses of nivolumab.
She reports redness and itching all over her chest and back.

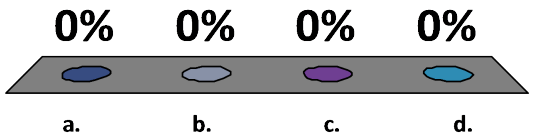
Which of the following may be the most helpful?

a. Diphenhydramine cream

b. Low-dose hydrocortisone cream

c. High-dose oral corticosteroids

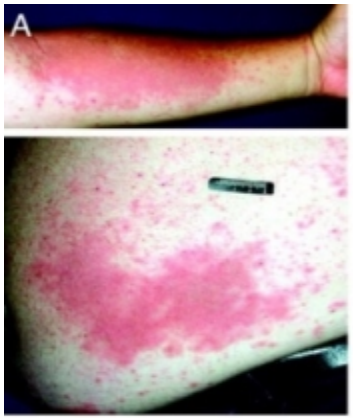
d. Hot shower

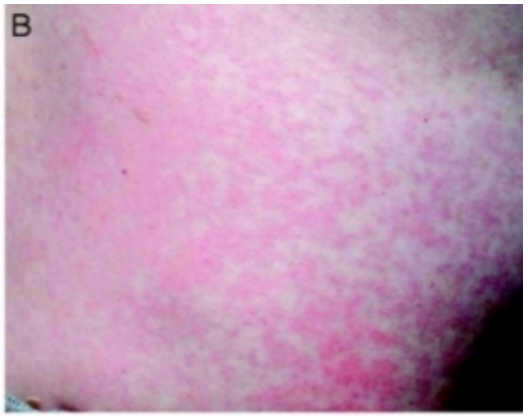


Case Presentation 4: LM

(Skin Toxicity Management)

- LM returns to clinic after topical low-dose steroids are prescribed.
  - Should she continued to receive nivolumab?





Dermatologic irAEs Overview

- Common irAEs
  - Mostly low grade
  - Rash , pruritus, and vitiligo
  - Most resolve with symptomatic therapy: moisturizers, diphenhydramine, hydroxyzine
  - If you use corticosteroids, watch out for flare
  - T-cell infiltrate seen on biopsy specimens of the skin

Case Presentation 5: CM

(Endocrine Toxicity Management)

- CM is a 52 yo male with PMH of type 2 diabetes.
- He is found to have a palpable axillary mass and ultimately diagnosed with stage IIIB melanoma and is started on nivolumab 3 mg/kg.
  - Week 2 of therapy he reports one week of low grade fever (100 °F) and body aches.
  - The heart monitor on his watch has shown his resting heart rate to be 80-90's when it's usually in the 60's
  - He also has been experiencing fatigue (but still going to work) as well as queasiness but eating okay
  - Current temp is 36.8 °C, BP 113/72 mmHg, HR 99 BPM, and RR 18
  - Exam shows tachycardia but otherwise unremarkable

Case Presentation 5: CM

(Endocrine Toxicity Management)

- Lab work
  - Na 138 mmol/L, K 4.7 mmol/L, CO^2 23, Glucose 270 mg/dL, sCR 0.86 mg/dL,
  - Total bilirubin 1.1, AST 153 U/L, ALT 96 U/L, LDH 210 U/L
  - Cortisol 4.9 mcg/dL, ACTH less than 5 pg/mL(1300 draw)
  - TSH 0.03 mIU/L, Free T4 greater than 5.5 ng/dL, T3 670 ng/dL

- Diagnosis?
  - Thyrotoxicosis
  - Grade 1 hepatitis
  - Type 1 Diabetes mellitus

TSH=thyroid stimulating hormone, T4=thyroxine, T3=triiodothryonine, ACTH=adrenocorticotropic hormone, sCR = serum creatinine, TB =total bilirubin

Endocrine irAEs Overview

- Hyperthyroidism, hypothyroidism, hypopituitarism, type 1 diabetes mellitus
- Measure TSH, free T4, ACTH, cortisol
- FSH, LH, and testosterone
- Consider ACTH stimulation studies
- Can you treat when endocrinopathies develop?

TSH=thyroid stimulating hormone, T4=thyroxine, ACTH=adrenocorticotropic hormone, FSH=follicle stimulating hormone, LH=luteinizing hormone

Case Presentation 5: CM

(Endocrine Toxicity Management)

- Labs take a few hours – Do you treat while waiting?
- Management of Endocrinopathies
  - Remember endocrinopathies are permanent
  - Beta Blockade
  - Consider Methimazole
  - Endocrinologists are my new best friend! ☺
    - Complete pituitary panel – AM ACTH, Cortisol, LH, FSH, Prolactin, Testosterone (wnl)
    - TSH Receptor Ab – less than 0.90 (wnl)
    - Thyroid Stimulating Immunoglobulin 97% (wnl)
    - Glutamic Acid Decarboxylase Antibody 5.9 (high)
    - Islet Cell Antibody IgG wnl
    - Started on Insulin
    - Long term, will develop hypothyroidism and require long-term thyroid hormone replacement.

Endocrine irAEs Overview

37 year-old CF with Stage IIIC resected melanoma s/p 3 doses of adjuvant ipilimumab 10 mg/kg presents with severe headaches

65 year-old CM with Stage IV melanoma s/p 2 doses of ipilimumab 3 mg/kg + nivolumab 1 mg/kg presents with severe fatigue, polyuria/polydipsia

61 year-old CM with Stage IV melanoma s/p 3 doses of ipilimumab 3 mg/kg + nivolumab 1 mg/kg presents with SOB and palpitations

30 year-old CF with Stage IV melanoma s/p 4 doses of pembrolizumab presents with low TSH, high T4 on routine labs

50 year-old CM with Stage IIIC resected melanoma on adjuvant trial of ipilimumab vs. nivolumab presents with fatigue

s/p=status post, SOB=shortness of breath

Comparison of Endocrine irAEs

- Meta-analysis of 38 randomized clinical trials with a total of 7551 patients
  - PD-1 inhibitor monotherapy
  - PD-L1 inhibitor monotherapy
  - CTLA-4 inhibitor monotherapy (ipilimumab)
  - Combination PD-1 and CTLA-4 inhibitors
- Results
  - Combination therapy had the highest rate of hypothyroidism (OR 3.81, $p<0.001$) and hyperthyroidism (OR 4.27, $p=0.001$) compared with ipilimumab alone
  - PD-1 inhibitor-treated patients had a higher risk of developing hypothyroidism (OR 1.89, $p<0.03$) compared with ipilimumab
  - Risk of hyperthyroidism (not hypothyroidism) was higher with PD-1 inhibitors compared with PD-L1 inhibitors (OR 5.36, $p=0.002$)
  - Hypophysitis was more common with ipilimumab than PD-1 inhibitors.

OR= Odds ratio

Barroso-Sousa R et al. *JAMA Oncol*. 2017; published online 9/28/2017.

Case Presentation 6: LY

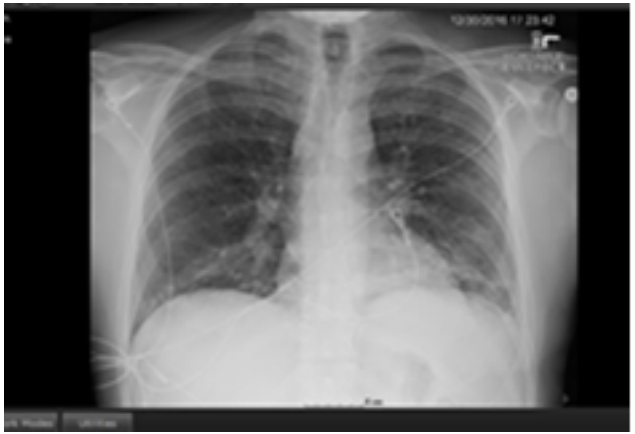
(Pulmonary Toxicity Management)

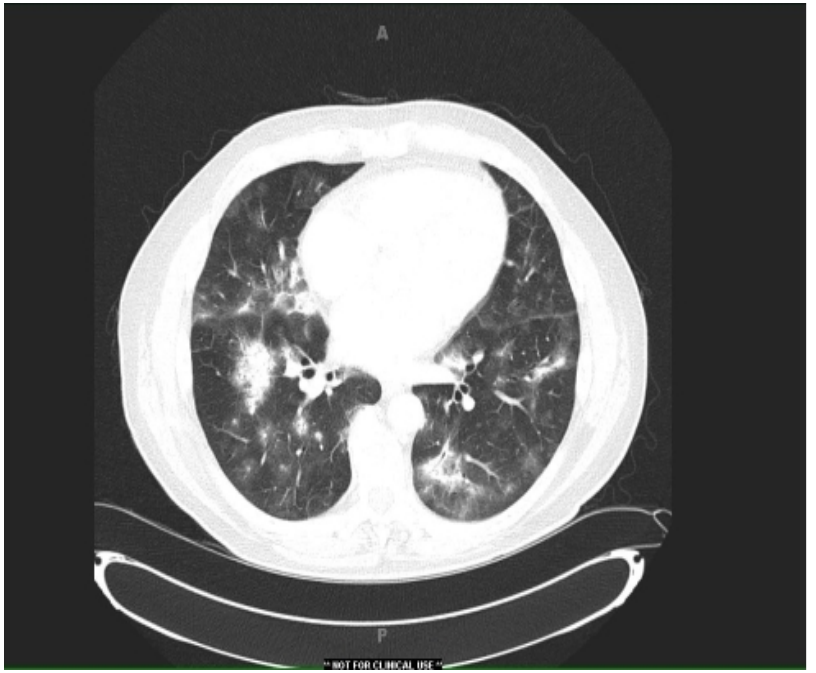
LY is a 54 yo male who presented with new onset seizures. He was found to have a 1.5 cm brain metastasis. CT shows diffuse disease in liver and retroperitoneum.

- Neurosurgery resects the brain lesion which is positive for melanoma.
- Receives stereotactic radiosurgery to the postoperative bed and starts pembrolizumab.
- After four doses, imaging shows partial response.
- After fifth dose, patient calls with new SOB, cough, low-grade fevers (100 °F)
- He comes to the clinic with the following vital signs:
  - Temp 37.8 °C, BP 109/68 mmHg HR 98 BPM, RR 20, Oxygen 92% Room Air
  - Physical examination: Tachypnea, coughing with deep inspiration, bilateral crackles

What do you do next?

Case Presentation #5: RC





Pneumonitis irAEs Overview

- Occurs with both ipilimumab (1%) and PD-1 antibodies, higher rate with PD-1 antibodies (3% of melanoma patients)
- Patients present with SOB, cough, hypoxia
- Grade 1 may appear on scans without symptoms
- For symptomatic patients
  - Rule out other causes
  - Consider bronchoscopy
  - Corticosteroids (1 mg/kg) either IV methylprednisolone or oral prednisone with prolonged taper for symptomatic cases

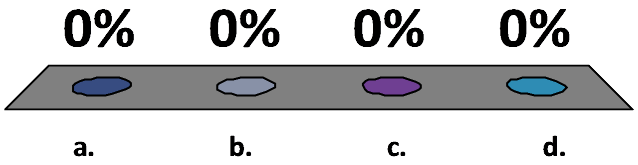
Beck KE et al. *J Clin Oncol*. 2006; 24:2283-9.

Case Presentation 6: LY

(Pulmonary Toxicity Management)

LY is ultimately admitted for further management. What is the recommended course of treatment?

a. Start IV antibiotics and start corticosteroids if no improvement
b. Perform bronchoscopy for diagnosis and start appropriate subsequent treatment
c. Start IV antibiotics and IV corticosteroids for pneumonitis with possible pneumonia
d. Start IV corticosteroids for pneumonitis



Case Presentation 7: PD

(Hepatotoxicity Management)

- PD is a 66 year old female (60 kg) with a history of Stage IIIC melanoma that metastasized to the right groin from right lower leg primary in 2015. After resection, she was followed with observation.
- 2/2017 she presented with headache and MRI showed a solitary brain metastasis which was treated with stereotactic radiosurgery (SRS).
  - CT showed disease in liver and pelvic lymph nodes.
- 3/2017: Initiated on ipilimumab 3mg/kg + nivolumab 1mg/kg, received three doses of each
- 5/2017: Presented to outside hospital with nausea and vomiting:
  - Lab work: AST 544 U/L, ALT 892 U/L, AP 281 mcg/L, TB 1.1

AP=alkaline phosphatase

Hepatotoxicity

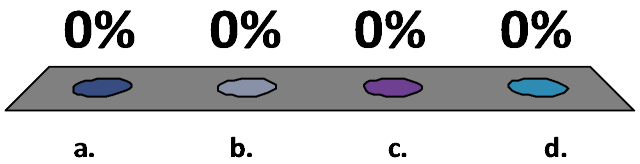
- Most cases are asymptomatic and found on lab tests only
- Especially with known liver disease, but rule out obstruction/disease as cause
- Monitor liver function tests (LFTs) every 3 weeks
  - If greater than 5x upper limit of normal range and increasing bilirubin, treatment with corticosteroids is indicated
  - Grade 1 – Can treat and monitor liver enzymes
  - Grade 2 – Withhold dose, recheck in 3-5 days, if continues to increase, start steroids
- Fulminant liver failure has been reported, but typically fully reversible

Case Presentation 7: PD

(Hepatotoxicity Management)

How should PD be managed?

a. Start oral corticosteroids 1mg/kg
b. Check liver imaging, if no obstruction, start oral corticosteroids 1mg/kg
c. Check liver imaging, if no obstruction, recheck labs in one week
d. Check liver imaging, if no obstruction, give corticosteroid dose pack



Case Presentation 7: PD

(Hepatotoxicity Management)

- PD was started on prednisone 60mg/day
- Liver enzymes normalized after two weeks and prednisone taper was initiated
  - How long do you taper?
  - How often do you check labs?
- When she was down to prednisone 20mg/day, AST rose to 200 U/L, ALT 120 U/L, total bilirubin within normal limits
  - Now what?

Case Presentation 7: PD

(Hepatotoxicity Management)

How should refractory hepatitis be treated?

a. Increase prednisone back to 60 mg/day, repeat taper once liver enzymes normalize
b. Continue taper, patient is asymptomatic.
c. "Increase prednisone back to 60 mg/day, add mycophenolate 1000 mg orally twice daily
d. Increase prednisone back to 60 mg/day, give one 5-mg/kg dose of infliximab IV

Neurotoxicity

- Take all neurologic symptoms seriously
- Rule out brain, spine disease as cause
- Ask for help from specialists!
- Peripheral neuropathy is most common
- Guillain-Barre and myasthenia gravis have been reported
- Always stop treatment in any serious neurotoxicity

Does occurrence of adverse effects correlate with treatment outcomes?

- Retrospective trial of 298 patients with metastatic melanoma treated with ipilimumab 3 mg/kg at Memorial Sloan Kettering Cancer Center
- Immune-related adverse events
  - 19% discontinued treatment (most common: diarrhea)
  - 35% of patients required corticosteroids
  - 10% of patients required infliximab
- Overall survival and time to treatment failure were not associated with immune-related adverse events or treatment with corticosteroids

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

Pearls in Managing irAEs

- Patient education is needed for early recognition of irAEs
- Nonspecific complaints might reflect endocrine (pituitary) toxicity
- Corticosteroids are effective – do not taper too quickly
- Consider infliximab or mycophenolate mofetil (MMF) in refractory cases
- Combination immunotherapies are associated with higher toxicity rates than single agent immunotherapy, but similar types of toxicities are seen
- Watch out for multiple irAEs in one patient, especially on combination (CTLA-4/PD-1 inhibitor) therapy
- Onset of irAEs in combination immunotherapy may be earlier than typically seen with single agent immunotherapy
- Consider prophylaxis if prolonged corticosteroids are required

Key Takeaways

- Key Takeaway #1
  - The role of immunotherapy in both solid tumors and hematologic malignancies continues to rapidly evolve
- Key Takeaway #2
  - Continued research into predictive biomarkers, such as PD-L1 expression, MSI status and mutation burden is needed to balance clinical benefit and toxicity from immunotherapy
- Key Takeaway #3
  - Immune-related toxicities are unique to these agents and require rapid recognition and treatment commonly involving corticosteroids

Selected Resources

- Nishino M, et al. Monitoring immune-checkpoint blockade: response evaluation and biomarker development. *Nat Rev Clin Oncol*. 2017(ahead of print).
- Weber JS, et al. Toxicities of immunotherapy for the practitioner. *J Clin Oncol*. 2015; 33:2092-9.

Faculty Discussion and Questions

- **Orlando Audience**
  - P R I N T your questions on a question card and a staff monitor will pick it up **OR**
  - Proceed to nearest microphone to ask your question
- **Webinar audience**
  - Expand control panel (click on orange arrow) and type in your question