

Understanding the Pharmacology of Immunotherapy: A Look at the Future in Managing Difficult-to-Treat Cancers

Proceedings of a Midday Symposium and Live Webinar at the
51st ASHP Midyear Clinical Meeting and Exhibition

Originally presented Tuesday, December 6, 2016
Las Vegas, Nevada

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This activity is sponsored and planned by the American Society of Health-System Pharmacists (ASHP).

Supported by an educational grant from Merck



**Understanding the Pharmacology of Immunotherapy:
A Look at the Future in Managing Difficult-to-Treat Cancers**

Agenda

11:30 a.m. – 11:35 a.m.

Welcome and Introductions

Christine M. Walko, Pharm.D.

11:35 a.m. – 11:45 a.m.

The Evolution of Immunotherapy: Past and Present

Christine M. Walko, Pharm.D.

11:45 a.m. – 12:20 p.m.

Current Place in Therapy for Solid Tumors and Lymphoma

Ragini R. Kudchadkar, M.D.

12:20 p.m. – 12:35 p.m.

Recognizing and Managing Immune-Related Adverse Events

Ragini R. Kudchadkar, M.D.

12:35 p.m. – 12:50 p.m.

Personalizing Therapy: Potential Biomarkers and Unique Patient Considerations

Christine M. Walko, Pharm.D.

12:50 p.m. – 1:00 p.m.

Faculty Discussion and Audience Questions

All Faculty

Faculty

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

Personalized Medicine Specialist

Moffitt Cancer Center

Associate Professor

University of South Florida Morsani College of Medicine

Tampa, Florida

Ragini Kudchadkar, M.D.

Assistant Professor

Department of Hematology and Medical Oncology

Associate Director

Hematology and Medical Oncology Fellowship Program

Winship Cancer Institute

Emory University School of Medicine

Atlanta, Georgia

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- Christine M. Walko, Pharm.D., BCOP, FCCP, declares that she has received honorarium from Bristol-Myers Squibb and Merck for participation in the Institute for Clinical Immuno-Oncology's melanoma board.
- Ragini Kudchadkar M.D., declares that she has previously served on an advisory board for Bristol-Myers Squibb.
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Activity Overview

This activity will explore the growing role of immunotherapy in the treatment of solid tumors and hematologic malignancies. The focus will center upon the evolution of immunotherapy and its role in cancer including the place in therapy for novel immunotherapies such as the inhibitors of CTLA-1, PDL1, and PD-1 as well as toxicity and management of diverse patients receiving therapy. Discussion will include novel indications in solid tumors as well as lymphomas, rationale and evidence of combination therapies and future directions for personalized therapy including biomarker identification and cost considerations.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Review the current state of immunotherapy in the role of cancer treatment, including agents, expanded indications, and place in patient care for solid tumors and lymphomas.
- Compare the pharmacology of immunotherapy agents (including interleukin 2, ipilimumab, pembrolizumab, and nivolumab) and describe their place in therapy both as single agents and in combination regimens.
- Recommend best practices for toxicity management with the use of immunotherapy.
- Apply strategies for the appropriate selection of immunotherapy in patient scenarios, including consideration of biomarkers and unique patient characteristics such as access to care.

Additional Educational Opportunities about Immunotherapy Coming in 2017

- **Ask the Experts webinar** – Faculty will explore issues raised by participant questions in today’s symposium (1 hour CPE). Available on-demand May 22, 2017

**For more information and to sign up to receive e-mail updates
about this topic, visit**

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This activity provides 1.5 hours (0.15 CEUs – no partial credit) of continuing pharmacy education credit.

Live Activity ACPE #: 0204-0000-16-472-L01-P

On-Demand Activity ACPE #: 0204-0000-16-472-H01-P



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**Understanding the Pharmacology of Immunotherapy:
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Faculty

Christine M. Walko, Pharm.D., BCOP, FCCP, *Activity Chair*

Personalized Medicine Specialist

Moffitt Cancer Center

Associate Professor

University of South Florida Morsani College of Medicine

Tampa, Florida

Christine M. Walko, Pharm.D., BCOP, FCCP, is a Personalized Medicine Specialist at the DeBartolo Family Personalized Medicine Institute at the H. Lee Moffitt Cancer Center and is also Associate Professor at the University of South Florida Morsani College of Medicine in Tampa, Florida. She is also the Chair of the Clinical Genomics Action Committee (CGAC) and attending on the Personalized Medicine Clinical Service at H. Lee Moffitt Cancer Center. Dr. Walko received her Doctor of Pharmacy from Duquesne University in Pittsburgh. She completed a pharmacy practice residency at Virginia Commonwealth University Health System/Medical College of Virginia Hospitals in Richmond, Virginia. She also completed a Hematology/Oncology specialty residency at the University of North Carolina (UNC) Hospitals and Clinics and a Hematology/Oncology fellowship at the University of North Carolina School of Pharmacy in Chapel Hill, North Carolina. She is a board certified oncology pharmacist.

She has researched and published extensively in oncology therapy and has presented nationally and internationally on oncology and pharmacogenomics and other topics related to treating patients with cancer.

Understanding the Pharmacology of Immunotherapy: A Look at the Future in Managing Difficult-to-Treat Cancers

Ragini R. Kudchadkar, M.D.

Assistant Professor

Winship Cancer Institute of Emory University

Associate Director Hematology/Oncology Fellowship Program

Atlanta, Georgia

Ragini R. Kudchadkar, M.D., is Assistant Professor of Hematology and Medical Oncology at the Winship Cancer Institute of Emory University in Atlanta, Georgia. She also serves as Associate Director of the Hematology/Oncology Fellowship Program.

Dr. Kudchadkar completed her Bachelor of Science degree in Neuroscience and Behavioral Biology and her Doctor of Medicine degree from Emory University. After completing her Internal Medicine residency at Emory University she completed her Hematology and Medical Oncology Fellowship at the University of Colorado Health Sciences Center in Denver, Colorado.

Dr. Kudchadkar is a cutaneous oncologist specializing in drug development and clinical trials primarily for melanoma. Her other interests include how current melanoma therapies affect the natural immune function both in T-cells and B-cells. She is also interested in exploring new treatments for rare cutaneous disease such as advanced basal cell carcinoma, merkel cell carcinoma, and squamous cell carcinoma.

Dr. Kudchadkar is a member of the American Society of Clinical Oncology, the Society for Melanoma Research, and the American Association for Cancer Research. She has served on the National Comprehensive Cancer Network Melanoma guidelines committee. She has authored numerous book chapters, review articles, and peer-reviewed papers as well as presented nationally in melanoma and immunotherapy.

CE IN THE MIDDAY

Understanding the Pharmacology of Immunotherapy:
A Look at the Future in Managing Difficult-to-Treat Cancers

Christine M. Walko, Pharm.D., BCOP, FCCP, *Activity Chair*
Moffitt Cancer Center
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Learning Objectives

- Review the current state of immunotherapy in the role of cancer treatment, including agents, expanded indications, and place in patient care for solid tumors and lymphomas.
- Compare the pharmacology of immunotherapy agents (including interleukin-2, ipilimumab, pembrolizumab, and nivolumab) and describe their place in therapy both as single agents and in combination regimens.
- Recommend best practices for toxicity management with the use of immunotherapy.
- Apply strategies for the appropriate selection of immunotherapy in patient scenarios, including consideration of biomarkers and unique patient characteristics, such as access to care.

The Evolution of Immunotherapy: Past and Present

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

Melanoma Case: HR

- HR is a 60 year-old male who initially developed a right lateral chest wall lesion in November 1996 that was shown to be melanoma
 - Breslow depth: 2.2 mm
 - Clark level IV
 - Sentinel lymph node (SLN) mapping negative
- Underwent resection followed by observation
- August 2001: developed subcutaneous cheek and scalp nodules shown to be recurrent melanoma

- How should this patient be treated?

Management in 2000s: HR

- December 2001: treated with biochemotherapy
 - Cisplatin, dacarbazine, interferon, interleukin, and vinblastine
- February 2002: CT scan showed new pulmonary disease
- April 2002: started high-dose (HD) interleukin
 - 600,000 IU/kg every 8 hours x 14 doses (5 days on, 2 weeks off, repeat)
 - Patient decided to stop after course #2 dose #10, after significant hypotension and dopamine drip started

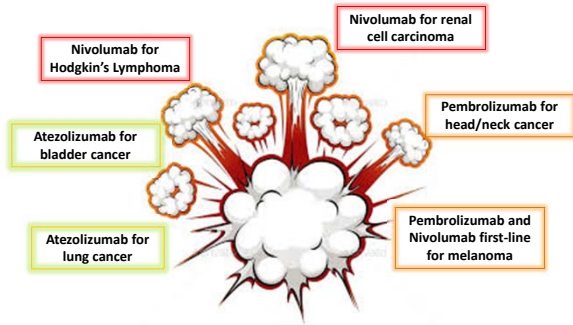
PD-1 or PD-L1 inhibitors are now FDA approved for all of the following disease states EXCEPT:



- a. Renal cell carcinoma
- b. Merkel cell carcinoma
- c. Urothelial carcinoma
- d. Hodgkin's lymphoma

PD-L1=programmed death ligand-1

Recent Approvals



History of Immunotherapy

| | Interleukin-2 | Ipilimumab | Nivolumab Pembrolizumab Atezolizumab |
|---|---|--|--|
| Immune target | Nonspecific T-cell growth factor | CTLA-4 | PD-1/PD-L1 |
| Approximate number of patients with \geq 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

The diagram illustrates the CTLA-4 and PD-1 pathways. On the left, a dendritic cell in a lymph node presents B7 to a T cell's CTLA-4 receptor. On the right, in systemic circulation, a T cell's PD-1 receptor binds to PD-L1 on a tumor cell.

- 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; 366:2517-19.

Nivolumab Phase I Trial Design

N=296 patients

- > Melanoma (n = 104)
- > Non-small cell lung cancer (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

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

BMS-936558

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

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.

Pembrolizumab FDA Approvals

| Indication | Approved Dose | Supporting Evidence | Citation |
|---|--------------------------|--|---|
| Unresectable or metastatic melanoma | 2 mg/kg IV every 3 weeks | Compared with ipilimumab, mPFS 4.1-5.5 vs. 2.8 months (p<0.001) and 6 month OS 68.4-74.1% vs. 58.2%. Note: pembrolizumab was dosed at 10 mg/kg either q2 or q3 weeks | Robert C et al. <i>N Engl J Med.</i> 2015; 372:2521-32. |
| Metastatic NSCLC whose tumors express PD-L1 | 2 mg/kg IV every 3 weeks | Compared with chemotherapy, mPFS 10.3 vs. 6.0 months (p<0.001) | Reck M, et al. <i>N Engl J Med.</i> 2016; ahead of print. |
| Metastatic NSCLC whose tumors express PD-L1 and have progressed on platinum therapy | 2 mg/kg IV every 3 weeks | Compared with docetaxel, mPFS 3.9 vs. 4.0 months but mOS 10.4 vs. 8.5 months (p=0.0008) | Herbst RS et al. <i>Lancet.</i> 2016; 387:1540-50. |
| Recurrent or metastatic head and neck cancer after progression on platinum therapy | 200 mg IV every 3 weeks | Non-comparative trial using a flat dose, showed 6 month PFS 23% and 6 month OS 59%. Overall, PD-L1 positive patients had improved response rates vs. non PD-L1 positive patients | <i>J Clin Oncol.</i> 2016; 34 ahead of print 9/19/2016. |

mPFS=median progression-free survival, OS=overall survival, mOS=median overall survival

Nivolumab FDA Approvals

| Indication | Approved Dose | Supporting Evidence | Citation |
|--|---|---|---|
| Unresectable or metastatic melanoma | 240 mg IV every 2 weeks | Compared with ipilimumab, mPFS 6.9 vs. 2.9 months (p<0.001) | Larkin J et al. <i>N Engl J Med.</i> 2015; 373:23-34. |
| Unresectable or metastatic melanoma WITH ipilimumab | 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks x 4 doses then 240 mg IV every 2 weeks | Compared with ipilimumab, mPFS 11.5 vs. 2.9 months (p<0.001). Similar mPFS to nivolumab alone for PD-L1 positive (14 months) but improved in PD-L1 negative (11.2 vs. 5.3 months) | Larkin J et al. <i>N Engl J Med.</i> 2015; 373:23-34. |
| Metastatic NSCLC after progression on platinum therapy | 240 mg IV every 2 weeks | Compared with docetaxel, mPFS 3.5 vs. 2.8 months (p<0.001) and mOS 9.2 vs. 6.0 months (p<0.001) | Borghaei H et al. <i>N Engl J Med.</i> 2015; 373:1627-39. |
| Advanced renal cell carcinoma after progression on anti-angiogenic therapy | 240 mg IV every 2 weeks | Compared with everolimus, mPFS 4.6 vs. 4.4 months, but mOS was 25 vs. 19.6 months (p=0.002) | Motzer RJ et al. <i>N Engl J Med.</i> 2016; 373:1803-13. |
| Classical Hodgkin lymphoma with progression following stem cell transplant and brentuximab vedotib | 3 mg/kg every 2 weeks | Single arm trial that showed objective response rate of 87% with 17% complete responses, 24 week PFS 86%, the trial remains ongoing | Ansell SM et al. <i>N Engl J Med.</i> 2015; 372:311-9. |

Atezolizumab FDA Approval

| Indication | Approved Dose | Supporting Evidence | Citation |
|---|--------------------------|--|--|
| Locally advanced or metastatic urothelial carcinoma following disease progression on a platinum regimen or within 12 months of neoadjuvant or adjuvant platinum therapy | 1200 mg IV every 3 weeks | Single arm trial (compared with historical overall response rate (ORR) of 10%), atezolizumab had an ORR of 15% (p=0.0058) with 27% of patients with >5% PD-L1 positivity having responses. Of the 45 responders, 84% have an ongoing response at 11.7 months of follow-up. | Rosenberg JE et al. <i>Lancet.</i> 2016; 387: 1909-20. |
| Metastatic NSCLC after progression on platinum therapy | 1200 mg IV every 3 weeks | The mOS was 12.6 months with atezolizumab and 9.7 months with docetaxel (p=0.04). Improvement was seen with increased PD-L1 expression. Further supported by the OAK trial with a 25% improvement in OS compared to docetaxel. | Fehrenbacher L et al. <i>Lancet.</i> 2016; 387: 1837-46. |

Current Status of Immunotherapy for Solid Tumors and Lymphoma
 Ragini R. Kudchadkar, M.D.

Current Options for Stage IV Melanoma

- Ipilimumab (ipi)
- Nivolumab or pembrolizumab
- Combination ipilimumab 3 mg/kg + nivolumab 1 mg/kg every 3 weeks x 4, followed by maintenance nivolumab 3 mg/kg every 2 weeks x 24
- BRAF/MEK combinations
- T-VEC

- HD IL-2
- Chemotherapy: biochemotherapy, carboplatin and paclitaxel, dacarbazine, temozolomide

Melanoma

| | |
|---|---|
| <p>FACTS</p> <ul style="list-style-type: none"> • PD-1 antibodies as single agents should be first-line over CTLA-4 antibodies • PD-L1 testing is not ready for prime time • Long term survival is seen with immunotherapy • Alternative agents such as HD-IL2 and chemotherapy should no longer be front-line | <p>QUESTIONS</p> <ul style="list-style-type: none"> • Should immunotherapy be first-line over BRAF inhibitors in BRAF-mutant melanoma? • Is combination ipilimumab/nivolumab preferred over single agent PD-1 antibody? • How long to continue PD-1 antibody treatment in responders? • Pseudoprogression or real progression? • Where does T-VEC fit in? |
|---|---|

Phase III Nivolumab +/- Ipilimumab

N = 945
Previously untreated patients with unresectable stage III or IV melanoma

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- Nivolumab 3 mg/kg every 2 weeks with placebo
- Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks x 4 followed by nivolumab 3 mg/kg every 2 weeks (cycle 3 and beyond)
- Ipilimumab 3 mg/kg every 3 weeks x 4 doses with placebo

• **Co-primary endpoints:** Overall survival and progression free survival (PFS)
• Tumor response assessed by RECIST v1.1 criteria

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

Ipilimumab + Nivolumab

- Tolerable dose: ipilimumab 3mg/kg + nivolumab 1 mg/kg
- 21/52 (40%) ORR
- “Rapid and Deep Responses”
- Toxicity
 - 93% ALL grades, treatment related
 - Grade 3/4 Toxicity 53%
 - Elevated lipase, aspartate aminotransferase (AST), alanine aminotransferase (ALT)
 - 21% dose-limiting
- PDL-1 Staining
 - 6/13 PD-L1 positive
 - 9/22 PD-L1 negative

Wolchok JD et al. *N Engl J Med.* 2013; 369:122-33.

Nivolumab + Ipilimumab: Tumor Response With Concurrent Therapy

ORR: 40%
Highest dose ORR: 53%
(by investigator-assessed irRC with confirmation)

Objective responses were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22) ($P > .99$)

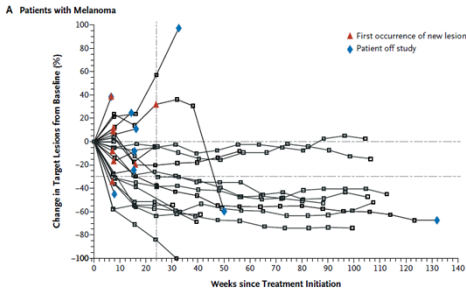
irRC=immune-related response criteria Wolchok JD et al. *N Engl J Med.* 2013; 369:122-33.

Phase III Nivolumab +/- Ipilimumab Summary

- Overall, the combination of nivolumab and ipilimumab resulted in improved mPFS compared with either agent alone
 - This was accompanied by an increase in all grade and grade 3 or 4 toxicities however
 - Biomarkers or other patient factors may be helpful to direct this therapy towards patients most likely to benefit
- PD-L1 expressing tumors treated with nivolumab or the combination had a similar mPFS while combination therapy benefited PD-L1 negative tumors more than single agent

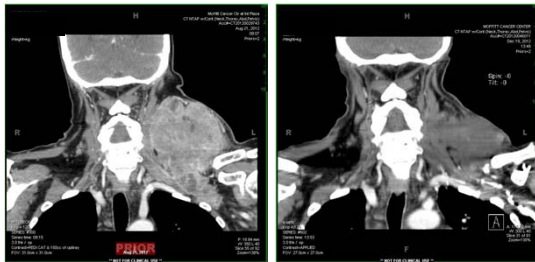
Larkin J et al. *N Engl J Med.* 2015; 373:23-34.

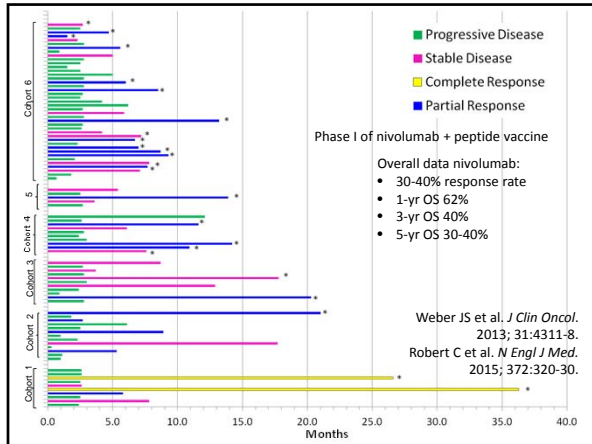
Responses Nivolumab - Melanoma



From The New England Journal of Medicine, Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer, Topalian SL, Hodi FS, Brahmner JR et al. Volume No. 366, Page No. 2448 Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Response to PD-1 antibody

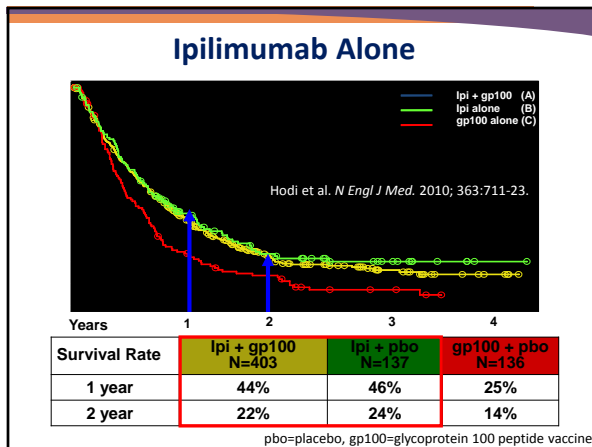




Pembrolizumab Alone

- Data similar to nivolumab
- Response rate (RR) 30-40%
- 5-year overall survival 30-40%
- Nivolumab followed by ipilimumab is clinically more beneficial (assumed to apply to pembrolizumab too)
- Why every 3 weeks vs. nivolumab, which is every 2 weeks?
- Is there a difference?

Weber JS et al. *Lancet Oncol.* 2016; 17(7):943-55
Hamid O et al. *N Engl J Med.* 2013; 369:134-44



Case Presentation: MC

- MC is a 33 year-old Caucasian female with a history of a 3.2 mm ulcerated melanoma of the right leg in 2014. At that time wide local excision (WLE) and SLN biopsies were negative.
- She was followed with observation until 2016, when routine imaging revealed multiple lung metastases.
- Biopsy confirmed metastatic melanoma which harbors the BRAF V600E mutation.

Case Question

What is the best front-line, approved treatment for MC?

- Ipilimumab
- Combination BRAF + MEK inhibitor
- Ipilimumab + nivolumab
- Single agent PD-1 antibody (either nivolumab or pembrolizumab)
- Either B, C, or D

Case Question

MC's pathology now returns with greater than 5% PD-L1 positivity. What is now the best front-line option?

- Ipilimumab
- Combination BRAF + MEK inhibitor
- Ipilimumab + nivolumab
- Single agent PD-1 antibody (either nivolumab or pembrolizumab)
- Either B, C, or D

Melanoma Current Status

- PD-1 inhibition is the backbone of immunotherapy in melanoma
- Combination treatments will be the future of immunotherapy in melanoma
- Adequate biomarkers have yet to be discovered
- The question of front-line treatment with targeted vs. immunotherapy has yet to be answered (NCT02224781)

Immunotherapy in all other cancers.....

Are PD-1 antibodies in the water at all cancer centers?

PD-1/PD-L1 antibodies

FDA Approvals

- Non-small cell lung cancer
- Recurrent head and neck cancer
- Urothelial carcinoma
- Renal cell carcinoma
- Hodgkin's lymphoma

Promising Data

- Hepatocellular Carcinoma
- Small cell lung cancer
- Merkel cell carcinoma
- Triple negative breast cancer
- Multiple myeloma
- Non-Hodgkin's lymphoma

Non-small Cell Lung Cancer

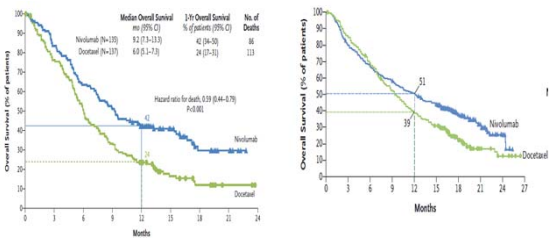
- Second-line only after progression despite platinum-based chemotherapy
- Nivolumab 240 mg IV every 2 weeks
- 1 yr OS 51% nivolumab (39% docetaxel)
- Nivolumab RR 19% vs. 12%
- PD-L1 expression predicts improved OS with pembrolizumab
 - mOS PD-L1 <1% 10.4 months
 - mOS PD-L1 >5% 18.2 months
 - mOS PD-L1 >10% 19.4 months
- Note: pembrolizumab improves PFS and OS in patients with NSCLC and 50% or greater PD-L1 expression

Reck M et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print].
 Borghaei H et al. *N Engl J Med.* 2015; 373:1627-39

Nivolumab Superior to Docetaxel in NSCLC

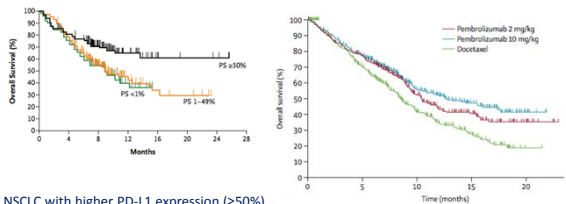
Squamous NSCLC

Non-Squamous NSCLC



Borghaei H et al. *N Engl J Med.* 2015; 373:1627-39.

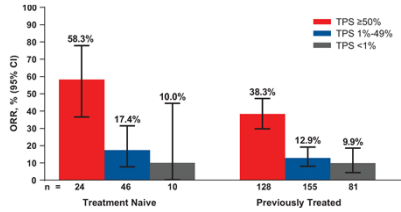
High PD-L1 Predicts Most Survival Benefit from Pembrolizumab in NSCLC: KEYNOTE-001 and 010



- NSCLC with higher PD-L1 expression (≥50%) have increased benefit from pembrolizumab
- Improved PFS, OS, RR, duration of response (DOR) for pembrolizumab over chemotherapy in NSCLC

Reck M et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print].
 Garon EB, et al. *N Engl J Med.* 2015; 372:2018-28.
 Herbst RS et al. *Lancet.* 2016; 387:1540-50.

High PD-L1 Predicts Better Response to Pembrolizumab (KEYNOTE-001)



Hui R et al. *J Clin Oncol*. 33(suppl): Abstract 9026. ASCO Annual Meeting, Chicago IL, 2016.

TPS=tumor proportion score

Metastatic Renal Cell Carcinoma

- Second-line after antiangiogenic therapy
- Nivolumab 240 mg IV every 2 weeks
- mOS 25 months nivolumab vs. 19.6 months everolimus
- RR 25% nivolumab vs. 5%

Motzer RJ et al. *N Engl J Med*. 2015; 373:1803-13.

Relapsed Hodgkin's Lymphoma

- 23 patients in the study
- Progression post stem cell transplantation (SCT) and brentuximab vedotin
- Nivolumab 3 mg/kg every 2 weeks
- RR 87%
- 17% complete response

Ansell SM et al. *N Engl J Med*. 2015; 372:311-19.


**Nivolumab in
Advanced Hodgkin's Lymphoma (HL)**

- Amplification of chromosome 9p24 is commonly seen in nodular sclerosis HL
 - Includes PD-L1, PD-L2, and JAK2
 - Ultimately results in overexpression of PD ligands on Reed-Sternberg cells
- 23 heavily pretreated patients with relapsed or refractory HL received nivolumab
 - Objective response: 87%
 - Partial response: 70%
 - Complete response: 17%
 - Median PFS at 24 weeks: 86%

Ansell SM et al. *N Engl J Med.* 2015; 372:311-19.

Case Presentation: AF

- AF, a 65 year-old Caucasian male with 50 pack-year history of tobacco use presents with new back pain.
- Imaging finds a 4 cm lung mass, hilar lymphadenopathy, adrenal and bone metastases.
- Biopsy confirms NSCLC without significant mutations (i.e., EGFR, ALK).

Case Question 

Should PD-L1 testing on the tumor be sent to determine the best treatment option?

a. True
b. False

Case Question

AF's tumor pathology comes back with 20% PD-L1 positivity. What is your best choice for front-line therapy?

- a. Nivolumab
- b. Pembrolizumab
- c. Platinum-based chemotherapy doublet
- d. Atezolizumab
- e. No treatment, palliative care alone is appropriate

Current Status of Immunotherapy

- PD-1 blockade is becoming the backbone of all oncology
- Role of PD-L1 testing is different depending on tumor type; currently the biggest role is in NSCLC
- Adding new agents to a PD-1 antibody backbone will be the future of oncology
- Will patients accept chemotherapy in this day and age, even if its proven better?

Recognition and Management of Immune-Related Adverse Events

Ragini R. Kudchadkar, M.D.

PD-1 antibodies (nivolumab or pembrolizumab) are not associated with life-threatening toxicity.



- a. True
- b. False

Mortality of Immunotherapy

- HD IL-2
 - Infection
 - Cardiac arrhythmias
- Ipilimumab
 - Colitis, perforation
- PD-1 antibodies
 - Pneumonitis

Morbidity of Immunotherapy

- Fatigue
- Rash/Pruritus
- Endocrinopathies
 - Pituitary dysfunction
 - Diabetes mellitus
- Patients are living longer, and some patients may be cured
 - Long-term adverse events may not yet be known

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.

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; 30:2691-97.

Case Presentation: JC

- JC is a 57 year-old, 100-kg, Caucasian male who just completed his third dose of ipilimumab.
- He calls your clinic with 10 nonbloody loose stools in the last 24 hours despite atropine/diphenoxylate.

Case Question



What is the best next step in management?

- Call in a 1 week steroid taper, such as a methylprednisolone dose pack.
- Hold further ipilimumab; the diarrhea will resolve on its own without further intervention as long as no additional treatment is given.
- Hold further ipilimumab; treat with steroids, and taper over 4-6 weeks if diarrhea improves. Restart ipilimumab once diarrhea is resolved.
- Discontinue ipilimumab. Start 1 mg/kg of prednisone or IV methylprednisolone and consider hospital admission.

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 steroids; can try **budesonide**
 - Follow closely for resolution

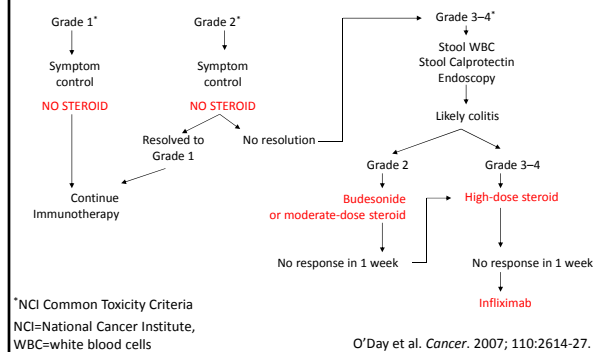
Gastrointestinal irAEs Overview

- 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 steroids (needs 4-6 week taper)
 - Can rarely lead to GI perforation (<1%) requiring surgery
- When do you retreat?

Gastrointestinal irAEs Timing

- With single-agent immunotherapy, mostly commonly seen about 6-8 weeks from 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)

Management Algorithm: Diarrhea



Case Question



JC is started on 1 mg/kg daily of steroids but continues to have abdominal pain and diarrhea after 2 days of steroids and bowel rest. What do you do next?

- Up the steroids to twice a day
- Give one dose of infliximab IV 5 mg/kg
- Nothing, JC needs more time to recover

Case Question



Alternatively, JC improved drastically on 1 mg/kg (100 mg) of prednisone and was discharged home with a steroid taper decreasing by 10 mg every 5 days. When he gets to 50 mg daily, he notices recurrent diarrhea with 6-8 bowel movements per day. What is the best next step?

- a. Increase prednisone to 100 mg daily, then restart taper once diarrhea resolves
- b. Increase prednisone to 100 mg daily, give one dose of IV infliximab at 5 mg/kg, then restart taper once diarrhea is resolved
- c. Add mycophenolate mofetil 1000 mg PO twice a day
- d. No changes needed, it is typical to have recurrent bouts of diarrhea when receiving ipilimumab

Can you skip the steroids and go straight to infliximab?

www.clinicaltrials.gov
NCT02763761

Dermatologic irAEs Overview

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

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=adrenocorticotrophic hormone, FSH=follicle stimulating hormone, LH=luteinizing hormone

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

Nivolumab-Induced Pneumonitis



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 demonstrate on scans without symptoms
- For symptomatic patients
 - Rule out other causes
 - Consider bronchoscopy
 - Steroids (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

Less Common irAEs

- Hepatotoxicity
 - Monitor liver function tests (LFTs) every 3 weeks
 - If greater than 5x upper limit of normal range and increasing bilirubin, treatment with steroids is indicated
 - Liver failure has been seen
 - Use of mycophenolate mofetil (MMF) if refractory to steroids
- Neurotoxicity
 - Any neurologic complaints should be taken seriously – Guillain-Barre, myasthenia gravis have been reported
 - Neuropathy is most common neurologic complaint

Does occurrence of adverse effects correlate with toxicity?

- Retrospective trial of 298 patients with metastatic melanoma treated with ipilimumab 3 mg/kg at Memorial Sloan Kettering
- Immune-related adverse events
 - 19% discontinued treatment (most common: diarrhea)
 - 35% of patient 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.

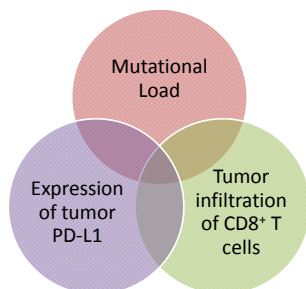
Pearls of irAEs

- Patient education for early recognition of irAEs
- Nonspecific complaints might reflect endocrine (pituitary) toxicity
- Corticosteroids are effective – do not taper too quickly
- Consider infliximab or 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) therapy
- Onset of irAEs in combination immunotherapy may be earlier than typically seen with single agent immunotherapy
- Consider prophylaxis if prolonged steroids are required

Personalizing Therapy: Potential Biomarkers and Unique Patient Considerations

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

Immunotherapy Tumor Markers



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

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.

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 **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)

Snyder A et al. *N Engl J Med*. 2014; 371:2189-99.
Rizvi NA et al. *Science*. 2015; 348:124-8.

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

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

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 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.

Biomarker Future Directions

- Given the 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

Case Presentation: RW

- RW is a 71 year-old female with rheumatoid arthritis previously receiving adalimumab and now on prednisone 10 mg daily.
- She presents with Stage IV melanoma with involvement of the lungs and liver.
- Her tumor is BRAF wild-type (WT).

Case Question



What are her options for treatment?

- a. Chemotherapy with dacarbazine (DTIC)
- b. No options given her autoimmune disorder
- c. Treatment with ipilimumab + nivolumab
- d. Treatment with nivolumab or pembrolizumab alone

Case Presentation: RW

- Given RW's poor prognosis from the melanoma, you elect to treat her with single agent pembrolizumab.
- Five days after her first dose, she presents to the emergency department (ED) with worsening joint pain and fever. Prednisone was increased to 15 mg/day with improvement of symptoms.
- Her rheumatologists tapers her down to 10 mg/day of prednisone after 5 days at the higher dose.
- She now presents to your clinic for her second dose of pembrolizumab. Do you retreat?

Immunotherapy in Autoimmune Diseases

- Clinical trials have traditionally excluded patients with preexisting autoimmune disorders
- Retrospective trial of 52 melanoma patients with preexisting autoimmune disorders treated with PD-1 inhibitors
 - Response rate = 33%
 - Flare requiring immunosuppression = 38%
 - Rheumatoid arthritis, polymyalgia rheumatica, Sjogren's syndrome, psoriasis, and immune thrombocytopenic purpura
 - No flare was seen in patients with gastrointestinal (n=6) or neurological (n=5) disorders
 - Discontinuation due to flare = 2 patients

Menzies AM et al. *Ann Oncol.* 2016; Sep 29 ahead of print.

Melanoma Case Revisited

- HR is a 60 year-old male who initially developed a right lateral chest wall lesion in November 1996 that was showed to be melanoma
 - Breslow depth: 2.2 mm
 - Clark level IV
 - Sentinel lymph node mapping negative
- Underwent resection followed by observation
- August 2001: developed subcutaneous cheek and scalp nodules shown to be recurrent melanoma

- How should this patient with newly diagnosed metastatic melanoma be treated?

Revisit Case: Future Therapy

- Tumor assessment for validated biomarkers:
 - BRAF positivity: BRAF- and MEK-directed therapy
 - Immunotherapy biomarker: PD-1 inhibitor alone versus combination therapy
- Genetic profile of tumor performed for predictors of response or resistance to future therapies
 - Enrollment in “basket trials” based on mutation profile

Key Takeaways

- Evidence supporting immunotherapy treatment options is rapidly developing and resulting in numerous approvals for PD-1 and PD-L1 inhibitors in both solid tumors and lymphoma
- Immune-related toxicities are unique to these agents and require rapid recognition and treatment commonly involving steroids
- The expression of PD-L1 on the tumor surface has been associated with benefit from immunotherapies in some tumors but more accurate, reliable biomarkers are being explored

Which of these changes in your practice are you likely to make after today's presentation?

- Read the current protocols for the use of immunotherapy at my institution.
- Discuss patient attitudes towards standard chemotherapy agents and immunotherapy agents with fellow staff.
- Recognize the adverse effects associated with immunotherapy.
- Discuss with colleagues potential strategies for managing the adverse effects associated with immunotherapy.
- Appropriately recommend FDA-approved immunotherapy options for the treatment of advanced cancers.

**Understanding the Pharmacology of Immunotherapy:
A Look at the Future in Managing Difficult-to-Treat Cancers**

Assessment Test



This assessment test has been provided as a study aid only. Follow the prompts at the end of the presentation to claim credit. Credit must be claimed within 60 days of completing the activity.

1. PD-1 or PD-L1 inhibitors are now FDA approved for all of the following disease states EXCEPT:
 - a. Renal cell carcinoma.
 - b. Merkel cell carcinoma.
 - c. Urothelial carcinoma.
 - d. Hodgkin's lymphoma.

2. Case Presentation: MC is a 33 year-old Caucasian female with a history of a 3.2 mm ulcerated melanoma of the right leg in 2014. At that time wide local excision (WLE) and SLN biopsies were negative.
She was followed with observation until 2016, when routine imaging revealed multiple lung metastases.
Biopsy confirmed metastatic melanoma which harbors the BRAF V600E mutation.

What is the best front-line, approved treatment for MC?
 - a. Ipilimumab.
 - b. Combination BRAF + MEK inhibitor.
 - c. Ipilimumab + nivolumab.
 - d. Single agent PD-1 antibody (nivolumab or pembrolizumab).
 - e. Either B, C, or D.

3. MC's pathology now returns with greater than 5% PD-L1 positivity. What is now the best front-line option?
 - a. Ipilimumab.
 - b. Combination BRAF + MEK inhibitor.
 - c. Ipilimumab + nivolumab.
 - d. Single agent PD-1 antibody (nivolumab or pembrolizumab).
 - e. Either B, C, or D.

4. Case Presentation: AF, a 65 year-old Caucasian male with 50 pack-year history of tobacco use presents with new back pain.
Imaging finds a 4 cm lung mass, hilar lymphadenopathy, adrenal and bone metastases.
Biopsy confirms NSCLC without significant mutations (i.e., EGFR, ALK).

Should PD-L1 testing on the tumor be sent to determine the best treatment option?
 - a. True.
 - b. False.

**Understanding the Pharmacology of Immunotherapy:
A Look at the Future in Managing Difficult-to-Treat Cancers**

5. AF's tumor pathology comes back with 20% PD-L1 positivity. What is your best choice for front-line therapy?
- Nivolumab.
 - Pembrolizumab.
 - Platinum-based chemotherapy doublet.
 - Atezolizumab.
 - No treatment, palliative care alone is appropriate.

6. PD-1 antibodies (nivolumab or pembrolizumab) are not associated with life-threatening toxicity.
- True.
 - False.

7. Case Presentation: JC is a 57 year-old, 100-kg, Caucasian male who just completed his third dose of ipilimumab.

He calls your clinic with 10 nonbloody loose stools in the last 24 hours despite atropine/diphenoxylate.

What is the best next step in management?

- Call in a 1 week steroid taper, such as a methylprednisolone dose pack.
 - Hold further ipilimumab; the diarrhea will resolve on its own without further intervention as long as no additional treatment is given.
 - Hold further ipilimumab; treat with steroids, and taper over 4-6 weeks if diarrhea improves. Restart ipilimumab once diarrhea is resolved.
 - Discontinue ipilimumab. Start 1 mg/kg of prednisone or IV methylprednisolone and consider hospital admission.
8. JC is started on 1 mg/kg daily of steroids but continues to have abdominal pain and diarrhea after 2 days of steroids and bowel rest. What do you do next?
- Up the steroids to twice a day.
 - Give one dose of infliximab IV 5 mg/kg.
 - Nothing, JC needs more time to recover.
9. Alternatively, JC improved drastically on 1 mg/kg (100 mg) of prednisone and was discharged home with a steroid taper decreasing by 10 mg every 5 days. When he gets to 50 mg daily, he notices recurrent diarrhea with 6-8 bowel movements per day. What is the best next step?
- Increase prednisone to 100 mg daily, then restart taper once diarrhea resolves.
 - Increase prednisone to 100 mg daily, give one dose of IV infliximab at 5 mg/kg, then restart taper once diarrhea is resolved.
 - Add mycophenolate mofetil 1000 mg PO twice a day.
 - No changes needed, it is typical to have recurrent bouts of diarrhea when receiving ipilimumab.

**Understanding the Pharmacology of Immunotherapy:
A Look at the Future in Managing Difficult-to-Treat Cancers**

10. Case Presentation: RW is a 71 year-old female with rheumatoid arthritis previously receiving adalimumab and now on prednisone 10 mg daily. She presents with Stage IV melanoma with involvement of the lungs and liver. Her tumor is BRAF wild-type (WT).

What are her options for treatment?

- a. Chemotherapy with dacarbazine (DTIC).
- b. No options given her autoimmune disorder.
- c. Treatment with ipilimumab + nivolumab.
- d. Treatment with nivolumab or pembrolizumab alone.
- e. Either A or D.