

# Ask the Experts: The Rapid Evolution of Immunotherapy for Melanoma: Translating Science to Patient Care

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**Presented as a Live Webinar**

Monday, March 23, 2015  
1:00 p.m. – 2:00 p.m. ET

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Planned by ASHP Advantage and supported by an educational grant from Merck.

# Ask the Experts: The Rapid Evolution of Immunotherapy for Melanoma: Translating Science to Patient Care

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## Activity Overview

This activity will describe the use of and outcomes with agents that stimulate immune function for the treatment of melanoma and other cancers. Prior experiences with interferon and interleukin will be compared with more recent data with immune checkpoint inhibitors including the CTLA-4 inhibitor ipilimumab and the PD-1 inhibitors pembrolizumab and nivolumab. Recent information on disease outcomes and adverse event management will be discussed, and practical, applicable strategies for medication selection and monitoring will be provided.

The content of this activity is based on questions raised by participants in a recent educational symposium on this topic as well as clinical aspects of treating patients with melanoma that faculty want to discuss further..

## Learning Objectives

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

- Examine historical and novel immunotherapy agents, pathways, and approaches for melanoma treatment.
- Use clinical information to select therapies and manage patients with melanoma including adverse event recognition and interventions.

## Continuing Education Accreditation



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-15-422-L01-P for the live activity and ACPE activity #0204-0000-15-422-H01-P for the on-demand activity).

Participants will process CPE credit online at <http://elearning.ashp.org/my-activities>, with the option of printing a CE certificate. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home study activity.

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## Activity Faculty

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

Clinical Pharmacogenomic Scientist

Moffitt Cancer Center

Associate Professor

University of South Florida Morsani College of Medicine

Tampa, Florida

Christine M. Walko, Pharm.D., BCOP, FCCP is Clinical Pharmacogenetics Scientist at the DeBartolo Family Personalized Medicine Institute and Clinical Scientist in the division of population science 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 Co-Chair of the Clinical Genomics Action Committee (CGAC) 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.

Prior to her current position, Dr. Walko was clinical assistant professor, Division of Pharmacotherapy and Experimental Therapeutics in the Institute of Pharmacogenomics and Individualized Therapy at the University of North Carolina Eshelman School of Pharmacy and Director of the Clinical Trial Unit Clinical Pharmacology Lab at the North Carolina Cancer Hospital at University of North Carolina Hospitals and Clinics Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Dr. Walko is a member of ASHP and is a Fellow of the American College of Clinical Pharmacy (ACCP) and has served as Oncology PRN president elect and secretary/treasurer for ACCP. She is also a member of the Hematology and Oncology Pharmacists Association (HOPA), the American Society of Clinical Oncology (ASCO) and the North Carolina Oncology Pharmacists Association. Dr. Walko has also served as president and secretary/treasurer at the Triangle College of Clinical Pharmacy. She serves on the International Society of Geriatric Oncology (SIOG) Task Force on Oral Cytotoxic Chemotherapy Dosing in the Elderly and is faculty for the Global Resource for Advancing Cancer Education (GRACE). Dr. Walko has received the teacher of the year award at the UNC Eshelman School of Pharmacy multiple times.

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.

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### **R. Donald Harvey, Pharm.D., FCCP, BCOP**

Associate Professor, Hematology/Medical Oncology  
Director, Phase 1 Clinical Trials Section  
Winship Cancer Institute  
Emory University  
Atlanta, Georgia

R. Donald Harvey, Pharm.D., FCCP, BCOP is Director, Phase 1 Clinical Trials Section at Winship Cancer Institute of Emory University and Associate Professor, Department of Hematology and Medical Oncology at the Emory University School of Medicine in Atlanta, Georgia. Dr. Harvey also serves as Co-chair of the Data Safety and Monitoring Committee and as a Pharmacology representative on the Clinical and Translational Research Committee for the cancer center, as well as preceptor for the Emory PGY-2 oncology residency.

He received his Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees from the University of North Carolina (UNC) in Chapel Hill. He subsequently completed a pharmacy practice residency at the University of Kentucky Medical Center and College of Pharmacy and a Hematology/Oncology specialty residency at UNC Hospitals and School of Pharmacy.

Dr. Harvey is a board certified oncology pharmacist and a fellow of the American College of Clinical Pharmacy (ACCP). He has authored or co-authored over 40 peer-reviewed publications, and is section editor for original research for the Journal of Hematology Oncology Pharmacy. He serves as a reviewer for the British Journal of Cancer, Journal of Pharmaceutical and Biomedical Analysis, Cancer, Annals of Oncology, Pharmacotherapy, and the Journal of Clinical Pharmacology. Dr. Harvey was President of the Hematology/Oncology Pharmacy Association (HOPA) from 2010-2013 and now serves as Vice Chair of the HOPA Research Foundation.

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- R. Donald Harvey, Pharm.D., FCCP, BCOP, has received research funding from Bristol Myers Squibb, Merck, Astra Zeneca, Genentech, and Novartis.
- All other faculty and planners report no financial relationships relevant to this activity.

## CE IN THE MIDDAY

### Ask the Experts: The Rapid Evolution of Immunotherapy for Melanoma: Translating Science to Patient Care

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## Disclosures

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## Learning Objectives

- Examine historical and novel immunotherapy agents, pathways, and approaches for melanoma treatment.
- Use clinical information to select therapies and manage patients with melanoma including adverse event recognition and interventions.

## Patient Case

- RT is a 48 year old man with localized (stage II) melanoma diagnosed in 2012, and treated with surgical resection and observation.
- He presents today after surveillance CT scans showed new lung lesions, with subsequent biopsy-confirmed melanoma.
- He is BRAF mutation negative, and otherwise healthy
- Questions
  - What options are available for his treatment?
  - How should therapy selection for his metastatic disease be approached?
  - What is the role of immunotherapy in his care?

## Cancer and Immune Evasion

- Individual cells and tumors have capacity to avoid immune surveillance from early in development
- Methods used
  - Production of immunosuppressive cytokines (e.g., TGF- $\beta$ , IL-4, IL-6, IL-10)
  - Increase number and function of immune suppressor cells (e.g., macrophages, regulatory T cells [Tregs])
  - Changes in cell signaling that leads to cancer cell death (e.g., increased IDO, reduced MHC receptors)
  - Limit immune effectors and create inhibitory checkpoints

IDO=indoleamine 2,3-dioxygenase  
MHC=major histocompatibility complex

## General Immunotherapy Approaches

- Active
  - Vaccination
    - Autologous
    - Allogeneic
  - Cytokines
    - Interferon, interleukin-2, GM-CSF
- Passive
  - Conventional naked (e.g., rituximab) and loaded (e.g., ado-trastuzumab emtansine) monoclonal antibodies
- Passive leading to active
  - Ipilimumab, pembrolizumab, nivolumab

## Current Immunotherapies in Melanoma

- Direct immune stimulation
  - Interleukin-2 (IL-2) used for metastatic disease
  - Interferon alfa-2B (IFN) for adjuvant therapy
- Inhibition of immune checkpoints
  - Cytotoxic T-lymphocyte antigen-4 (CTLA-4)
    - Ipilimumab approved for metastatic melanoma in 2011
  - Programmed cell death protein 1 (PD-1) receptor
    - Pembrolizumab approved for patients who failed ipilimumab in 9/4/2014
    - Nivolumab approved for same indication 12/22/2014

## Question

Which of the following statements is true about high-dose IL-2?

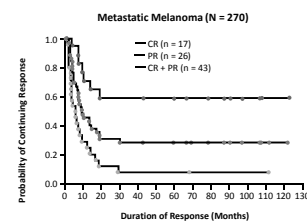
- It produces durable responses in 25% of patients.
- It can be considered for use in patients on hemodialysis.
- It should be given in an inpatient setting only.
- It is more effective than newer immunotherapies.

## High Dose (HD) IL-2 Therapy in Melanoma

- High-dose IL-2 benefits patients, but:
  - Toxic
  - Impractical: must be delivered as an inpatient
- Use limited to selected patients treated at experienced centers
  - No brain metastases, good organ function and performance status
- Efforts to develop more tolerable IL-2 based regimens unsuccessful
- Proof of principle that immunotherapy can produce durable benefit in patients with solid tumor malignancies

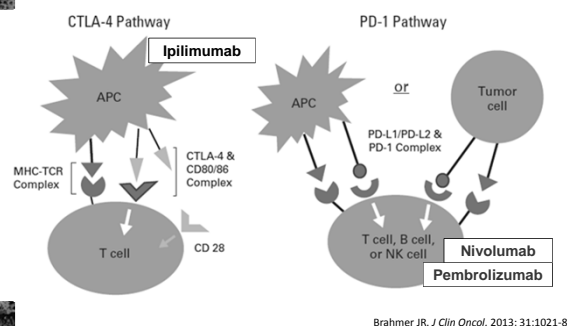
## HD IL-2 Therapy and Durable Responses

- HD IL-2 produces durable responses in up to 10% of patients with advanced melanoma
- Few relapses in patients responding for over 2.5 years (therefore, can be considered cured)
- FDA approved in 1997



Atkins MB et al. *J Clin Oncol*. 1999;17:2105-2116.

## CTLA-4 and PD-1 Pathways



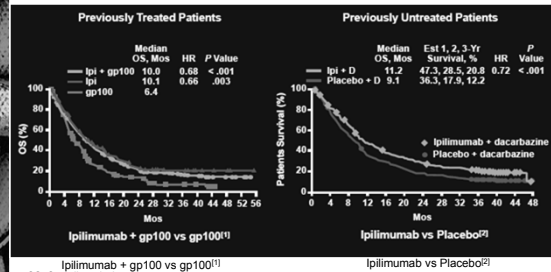
## Ipilimumab

- Fully human IgG1 monoclonal antibody to human cytotoxic T lymphocyte antigen 4 (CTLA-4)
  - Blocks binding of CTLA-4 to ligands CD80 and CD86 (B 7 family)
  - Results in upregulation of number and function of T lymphocytes
- Population – unresectable or metastatic melanoma
- Approved regimen = 3 mg/kg IV over 90 minutes Q3 weeks x 4 doses
- Trial comparing 3 mg/kg to 10 mg/kg completed enrollment
  - Overall survival endpoint results pending

## Ipilimumab

- Immune-mediated adverse events across trials
  - T cell activation and proliferation leading to enterocolitis (7%), hepatitis (1%), dermatitis (2%), neuropathy (1%), endocrinopathy (hypopituitarism – 4%)
- Monitor LFTs, thyroid function, chemistries before each dose
- Generally appear during induction
- Prednisone 0.5-2 mg/kg/day

## Ipilimumab in Metastatic Melanoma: Durable Survival



Adapted from Hodi FS et al. *N Engl J Med*. 2010; 363:711-723.  
Robert C et al. *N Engl J Med*. 2011;364:2517-2526.

## Ipilimumab: Immune-Related Adverse Events

System	Symptoms	Management
GI tract	Diarrhea Abdominal pain Dark, bloody stools	Moderate enterocolitis: hold ipilimumab, administer antidiarrheal. Persistent diarrhea (> 1 wk): systemic corticosteroids, 7-8 mg/kg/day; start methylprednisolone, permanently discontinue ipilimumab. Consider infliximab for corticosteroid-refractory patients
Skin	Rash (± itching) Blistering/peeling Oral sores	Moderate/nonlocalized rash: hold ipilimumab, start topical or systemic corticosteroids. Severe dermatitis: permanently discontinue ipilimumab, start corticosteroids
Liver	Jaundice Nausea/vomiting	Assess ALT/AST, bilirubin, and thyroid function before each dose and as necessary. Hold ipilimumab if ALT/AST > 2.5 x but ≤ 5 x ULN; permanently discontinue if ALT/AST > 5 x ULN or bilirubin > 3 x ULN. The immunosuppressant mycophenolate can be used for hepatotoxicity in corticosteroid-refractory patients.
CNS	Weakness in extremities Numbness/tingling Sensory changes	Moderate neuropathy: hold ipilimumab. New or worsening neuropathy: permanently discontinue ipilimumab. Consider corticosteroids
Endocrine	Headaches Fatigue Behavior/mood changes Menstruation changes Dizziness/light-headedness	Moderate endocrinopathy: hold ipilimumab, start corticosteroids. Endocrine abnormalities can be difficult to detect, due to nonspecific symptoms. Consider having an endocrinologist follow the patient
Eyes	Vision problems Irritation	Monitor for redness suggesting uveitis, treat with topical steroid eye drops

Ipilimumab adverse reaction management guide. Available at: <http://hcp.yervoy.com/pages/rem.s.aspx>.

## Ipilimumab Adverse Effects

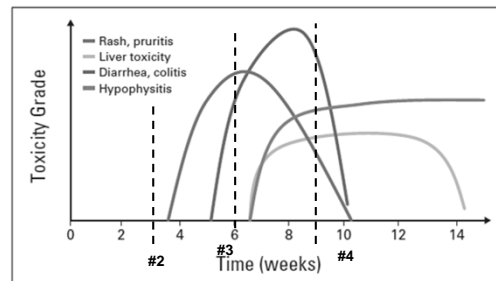
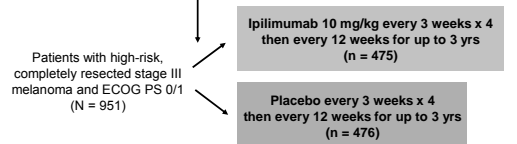


Fig 2. Kinetics of appearance of immune-related adverse event.

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

## EORTC 18071: Adjuvant Ipilimumab vs Placebo for Resected Stage III Disease

Stratified by stage (IIIA vs IIIB vs IIIC with 1-3 positive LN vs IIIC with ≥ 4 positive LN), region (North America, Europe, Australia)

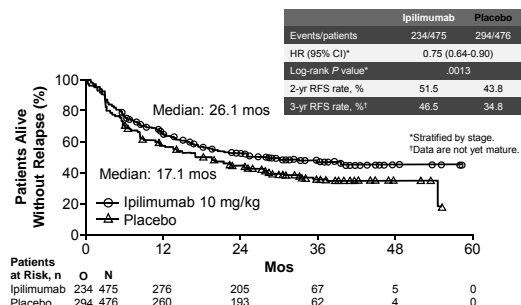


Primary endpoint: RFS per IRC (time to local, regional, distant metastasis, or death)

Secondary endpoints: OS, DMFS, AE profile, health-related QoL

Eggermont A et al. *J Clin Oncol*. 2014; 32:5s. (suppl; abstr LBA9008).

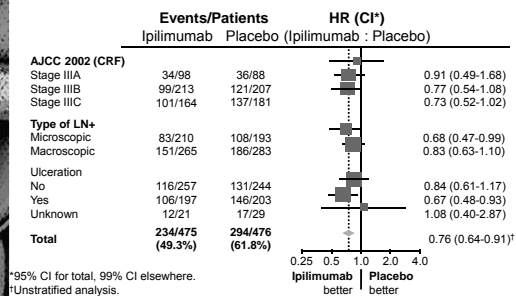
## Adjuvant Ipilimumab vs Placebo for Resected Stage III Disease: RFS



Eggermont A et al. *J Clin Oncol*. 2014; 32:5s. (suppl; abstr LBA9008).



## Ipilimumab vs Placebo for Resected Stage III Disease: RFS by Subgroup



Eggermont A et al. J Clin Oncol. 2014;32:5s. (suppl; abstr LBA9008).

## Ipilimumab vs Placebo for Resected Stage III Disease: irAEs

	Patients, %					
	Ipilimumab (n = 471)			Placebo (n = 474)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any irAE	90.4	36.5	5.5	38.6	2.3	0.2
Dermatologic	63.3	4.5	0	20.9	0	0
Rash	34.4	1.3	0	11.0	0	0
Gastrointestinal	46.3	14.9	1.1	17.7	0.6	0.2
Diarrhea	41.4	9.6	0	16.7	0.4	0
Colitis*	15.9	6.8	0.8	1.3	0.2	0
Endocrine	37.6	7.9	0.6	6.5	0	0
Hypophysitis	18.3	4.7	0.4	0.4	0	0
Hypothyroidism	8.9	0.2	0	0.8	0	0
Hepatic	25.1	7.9	2.8	4.4	0.2	0
LFT increase	19.7	3.8	1.5	4.0	0	0
Neurologic	4.5	1.1	0.8	1.9	0	0
Other	23.6	7.4	0.4	4.4	1.7	0

Eggermont A et al. J Clin Oncol. 2014; 32:5s. (suppl; abstr LBA9008).

## Adjuvant Ipilimumab Perspective

- Median RFS in resected stage IIIa-c melanoma: 17 mos with placebo to 26 mos with ipilimumab (HR: 0.75;  $P = .0013$ )
- Improvement seen for all stages, ulcerated primary or not, microscopic or macroscopic LN burden
- Grade 3/4 irAE rate: 42%
- Is the benefit worth the toxicity?

## Nivolumab Phase I Trial Design

**N=296 patients**

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

All patients had a ECOG performance status of  $\leq 2$  and measurable disease

### Phase 1 Dose Escalation of anti-PD-1 antibody

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

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-L1 predicted response rate
  - 0 of 17 responses in PD-L1 negative tumors
  - 9 of 25 responses in PD-L1 positive tumors

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

## Selected Toxicity

Toxicity	Anti-PD-1 Antibody all dose levels	
	All grade	Grade 3 and 4
Diarrhea	11%	1%
Infusion reaction	3%	1%
Hypothyroidism	2%	1%
Increased AST	4%	1%
Pneumonitis	3%	1% (3 deaths)
Skin Toxicity		
Rash	12%	0%
Pruritus	29%	1%
Vitiligo	8%	0%
Urticaria	2%	0%

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

## Clinical Development of Inhibitors of the PD-1 Immune Checkpoint

Target	Antibody	Molecule	Development Stage
PD-1	Nivolumab (BMS-936558)	Fully human IgG4	Approved in melanoma, squamous NSCLC
	Pembrolizumab (MK-3475)	Humanized IgG4	Approved in melanoma
	Pidilizumab (CT-011)	Humanized IgG1	Phase II multiple tumors
PD-L1	BMS-936559	Fully human IgG4	Phase I
	Medi-4736	Engineered human IgG1	Phase I
	MPDL-3280A	Engineered human IgG1	Phase I-II

## Question

In which of the following cancers have PD-1 antagonists shown promising clinical trial results?

- Non-small cell lung cancer
- Melanoma
- Hodgkin lymphoma
- All of the above
- None of the above

## Activity of Anti-PD-1/PD-L1 in Patients With Advanced Melanoma

Agent	Pts, n	ORR (at Optimal Dose), %	Grades 3/4 Tx-Related AEs, %	6-Mo PFS, %	12-Mo PFS, %	Median PFS, Mos	1-Yr OS, %	2-Yr OS, %
Nivolumab (anti-PD-1) <sup>[1-3]</sup>	104	31 (41)	22	41	36	3.7	62	43
Pembrolizumab (anti-PD-1) <sup>[4,5]</sup>	135	38 (52)	13	NA	NA	> 7	81	NA
BMS 936559 (anti-PD-L1) <sup>[6]</sup>	55	17	5	NA	NA	NA	NA	NA
MPDL3280A (anti-PD-L1) <sup>[7]</sup>	44	29*	36	43	NA	NA	NA	NA

\*Includes 4 patients with UM without a response.

- Topalian SL et al. *J Clin Oncol*. 2014; 32:1020-30. 2. Sznol M et al. ASCO 2013. Abstract 9006.
- Topalian SL et al. *N Engl J Med*. 2012; 366:2443-54. 4. Ribas A et al. ASCO 2013. Abstract 9009.
- Hamid O et al. *N Engl J Med*. 2013; 369:134-44. 6. Brahmer JR et al. *N Engl J Med*. 2012; 366:2455-65.
- Hamid O et al. ASCO 2013. Abstract 9010.

## Comparison of Anti-PD-1 Agents

	Pembrolizumab	Nivolumab
Initial FDA Approval Date	September 4, 2014	December 22, 2014
Type of Antibody	Humanized, , IgG4 kappa immunoglobulin	Human, IgG4 kappa immunoglobulin
Approved Dosing	2 mg/kg over 30 minutes every 3 weeks	3 mg/kg IV over 60 minutes every 2 weeks
Dose forms	50 mg lyophilized powder in single use vial and 100mg/4mL solution in single use vial	40 mg/4mL and 100 mg/10mL solution in single-use vial
Approved Indication	FDA accelerated approval for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor	

## When to Hold Anti-PD-1 Agents

Withhold therapy for:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Symptomatic hypophysitis (fatigue, headache)
- Grade 2 nephritis
- Grade 3 hyperthyroidism (pembrolizumab)
- AST/ALT >3 and ≤ 5 times ULN or total bilirubin >1.5 and ≤ 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction

Resume in patients whose adverse reactions recover to Grade 0-1

Keytruda [package insert]. County Cork, Ireland: Merck & Co., Inc; 2014  
Opdivo. [Package insert]. Bristol Myers Squibb, Princeton, New Jersey. 2014

## When to Permanently Discontinue Anti-PD-1 Agents

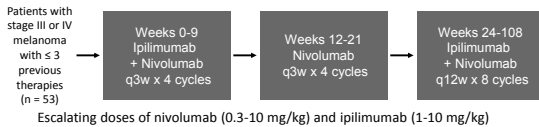
Permanently discontinue in cases of:

- Grade 3 or 4 pneumonitis, nephritis, or infusion-related reactions
- AST or ALT > 5 times ULN or total bilirubin > 3 times ULN
- Liver mets who begin treatment with Grade 2 AST or ALT, if increases by ≥ 50% relative to baseline and lasts for ≥1 week
- Inability to reduce corticosteroid dose to ≤10 mg of prednisone/day by 12 weeks
- Persistent Grade 2 or 3 adverse reactions that do not recover to Grade 0-1 within 12 weeks
- Any severe or Grade 3 treatment-related adverse reaction that recurs

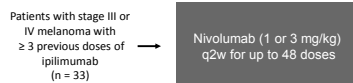
Keytruda [package insert]. County Cork, Ireland: Merck & Co., Inc; 2014  
Opdivo. [Package insert]. Bristol Myers Squibb, Princeton, New Jersey. 2014

## Nivolumab + Ipilimumab: Phase I Study

### • Concurrent therapy study design:

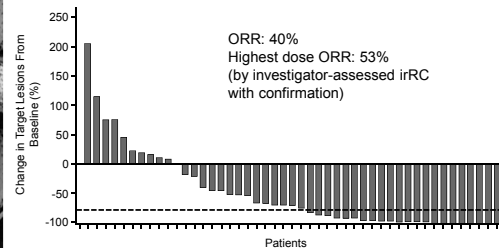


### • Sequenced therapy study design



Wolchok JD et al. *N Engl J Med.* 2013; 369:122-33.  
Wolchok JD et al. *ASCO* 2013. Abstract 9012.

## Nivolumab + Ipilimumab: Tumor Response With Concurrent Therapy



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

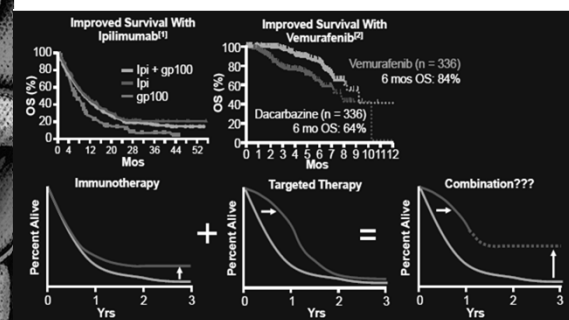
Wolchok JD et al. *N Engl J Med.* 2013; 369:122-33.

## Nivolumab + Ipilimumab Adverse Events

Treatment-Related AE, Number of Patients (%)	Concurrent All Cohorts (n = 53)		Sequenced All Cohorts (n = 33)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Any adverse event	49 (93)	28 (53)	24 (73)	6 (18)
Rash	29 (55)	2 (4)	3 (9)	0
Pruritus	25 (47)	0	6 (18)	0
Fatigue	20 (38)	0	3 (9)	0
Diarrhea	18 (34)	3 (6)	3 (9)	0
Nausea	11 (21)	0	1 (3)	0
Pyrexia	11 (21)	0	1 (3)	0
AST increase	11 (21)	7 (13)	0	0
ALT increase	11 (21)	6 (11)	1 (3)	0
Lipase increase	10 (19)	7 (13)	4 (12)	2 (6)
Amylase increase	8 (15)	3 (6)	1 (3)	1 (3)
Cough	7 (13)	0	2 (6)	0
Vomiting	6 (11)	1 (2)	0	0
Vitiligo	6 (11)	0	0	0
Headache	6 (11)	0	0	0

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

## Combining Immunotherapy and Targeted Therapy for Melanoma



Adapted from Hodi FS et al. *N Engl J Med.* 2010; 363:711-723.  
Chapman PB et al. *N Engl J Med.* 2011; 364:2507-2516.

## Ipilimumab + Vemurafenib Liver Toxicities in Phase I Testing

Patient Number	Doses of Ipilimumab Before ALT-AST Elevation, n	Time to Onset of ALT-AST Elevation After First Dose Ipilimumab, Days	Treatment	Time to Resolution of ALT-AST Elevation, Days	Toxicity Relapse With Repeated Ipilimumab
Cohort 1*					
4	1	21	Vem discontinued for 5 days then restarted with dose reduction; ipi permanently discontinued	4	NA
5	2	26	Vem discontinued for 4 days then restarted with dose reduction; ipi continued (2 doses)	6	No
6†	1	21	Vem discontinued for 5 days then restarted with dose reduction; ipi continued (1 dose)	6	No
8	1	19	Vem discontinued for 4 days then restarted with dose reduction; ipi continued (1 dose)	12	Yes
Cohort 2‡					
10	1	15	Vem discontinued for 7 days then restarted with dose reduction; ipi permanently discontinued (1 dose)	10	NA
16§	1	13	Vem and ipi permanently discontinued	20	NA

\*Cohort 1: 1-month run-in of single-agent vemurafenib 960 mg BID followed by 4 infusions of ipilimumab 3 mg/kg every 3 wks plus vemurafenib.

†Patient also had grade 2 increase in total bilirubin.

‡Cohort 2: vemurafenib 760 mg BID plus ipilimumab 3 mg/kg every 3 wks.

§Patient also had grade 3 increase in total bilirubin.


Ribas A et al. *N Engl J Med.* 2013;368:1365-1366.

## Immunotherapy Costs

- Assumptions: Most common or FDA labeled dosing and 80 kg patient

Agent	Regimen	Cost (3 months)	Comment
HD IL-2	720,000 U/kg IV every 8hr x 12 doses	\$44,352.42 per course (Emory average = 3 courses = \$133,057.26)	Hospitalization costs and supportive care not included
Ipilimumab	3 mg/kg IV every 3 weeks x 4 doses	\$155,128.84	200 mg + 50 mg vials
Pembrolizumab	2 mg/kg IV every 3 weeks	\$41,433.60	2 x 100 mg vials
Nivolumab	3 mg/kg every 2 weeks	\$41,437.44	2 x 100 mg vials + 40 mg vial

[www.utdol.com](http://www.utdol.com) monographs on specific agents, average wholesale price



## Conclusions

- Advances in understanding T cell biology have led to a greater number of agents that upregulate immune function.
- Novel agents and combinations continue to improve outcomes across all disease stages.
- Evolving development of existing and investigational agents means pharmacists will require continued education about use, adverse event prophylaxis and management, and cost implications.