

# **New and Emerging Strategies for the Treatment of Advanced Melanoma**

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Presented as a Midday Symposium and Live Webinar at the  
49<sup>th</sup> ASHP Midyear Clinical Meeting and Exhibition

Monday, December 8, 2014  
Anaheim, California

## **On-demand Activity**

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## Agenda

- 11:30 a.m. – 11:40 a.m. **Welcome and Introduction**  
Christine M. Walko, Pharm.D., BCOP, FCCP
- 11:40 a.m. – 12:00 p.m. **Pathophysiology of Melanoma and Drug Approval**  
R. Donald Harvey, Pharm.D., FCCP, BCOP
- 12:00 p.m. – 12:25 p.m. **Immunotherapy and Targeted Treatment**  
R. Donald Harvey, Pharm.D., FCCP, BCOP  
Christine M. Walko, Pharm.D., BCOP, FCCP
- 12:25 p.m. – 12:50 p.m. **Future of Melanoma Treatment**  
Christine M. Walko, Pharm.D., BCOP, FCCP
- 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***

Clinical Pharmacogenomic Scientist  
Moffitt Cancer Center  
Associate Professor  
University of South Florida Morsani College of Medicine  
Tampa, Florida

**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

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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.

### Activity Overview

According to the National Cancer Institute and the American Cancer Society, over 75,000 people will be diagnosed with melanoma in the United States in 2014, with 9710 deaths. The increasing number of people in the US over 65 along with longer life expectancy generally will lead to greater numbers of patients diagnosed with melanoma over the coming decade. Although knowledge about prevention of melanoma has become more prevalent, death due to advanced disease has doubled over the past 30 years. Inevitably, the aging US population and improvement in treatments will increase the number of patients with melanoma and present new challenges.

A number of novel treatments have been approved and are in development for patients with melanoma. Oral agents that target molecular drivers of the disease have produced robust response rates, however, they come with a number of challenges for patients and providers, specifically drug interactions, food effects, and unique side effects. Along with new oral agents, drugs that activate the immune system have also been approved for use, with impressive activity. These agents also have specific adverse event profiles that all pharmacists should be familiar with. Faculty will discuss current agents and regimens used to treat melanoma, highlighting recently approved agents and treatment controversies. Management principles and key resources for pharmacists will also be discussed.

### Learning Objectives

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

- Review the pathophysiology of BRAF-mutant melanoma.
- Design a first- line therapeutic plan for a patient who has BRAF-mutated metastatic melanoma.
- Compare and contrast the mechanism of action and toxicity profile of interleukin 2, ipilimumab, and pembrolizumab.
- Describe common adverse effects associated with immunotherapy as well as strategies for managing them.
- Discuss future directions in the treatment of melanoma therapy with regard to treatment options and tumor genomic sequencing.

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- **Available in 2015**

- **Ask the Experts Webinar.** Our expert faculty will focus on key questions received after the Midyear symposium. If you miss the live webinar in early 2015, plan to view the on-demand archive version later in 2015.
- **Engaging the Experts.** William Zellmer discusses key issues with the faculty from the Midyear Meeting symposium.
- **CE Discussion Guide.** Download and read the discussion guide to learn more about the topic.
- **e-Newsletter.** Download and read brief updates on this topic.
- **On-Demand Archive.** Captures the faculty presentations from the live symposium for those unable to attend the Midyear Clinical Meeting (1.5 hours CPE; individuals claiming CPE for the live activity or webinar are ineligible to claim credit for this activity).

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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 a live activity or completion of a home study activity.

**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.



**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.

CE IN THE MIDDAY


New and Emerging Strategies for the Treatment of Advanced Melanoma

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

Clinical Pharmacogenomic Scientist  
Moffitt Cancer Center  
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- Review the pathophysiology of BRAF-mutant melanoma.
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## CE IN THE MIDDAY

### Pathophysiology of Melanoma and Drug Approval

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

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Director, Phase 1 Clinical Trials Section  
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### Melanoma Epidemiology

- 3% of skin cancer cases
  - 80% of skin cancer deaths
- ~60,000 new US cases each year
- ~8,000 will die
- High cure rates if treated early
- 14% of patients with metastatic melanoma have 5-year survival rate

Miller AJ et al. *N Engl J Med*. 2006; 355: 51-65.

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### Risk Factors

- **UV Radiation**
- **Previous sunburns**
  - > 4 severe by 15 yr
- **Outdoor lifestyles**
- Age
- Male Gender
- Past hx of melanoma
- Xeroderma pigmentosum
- Dysplastic nevi
- Fair skin
- Family History of melanoma
- Immunosuppressed

Miller AJ et al. *N Engl J Med*. 2006; 355: 51-65.

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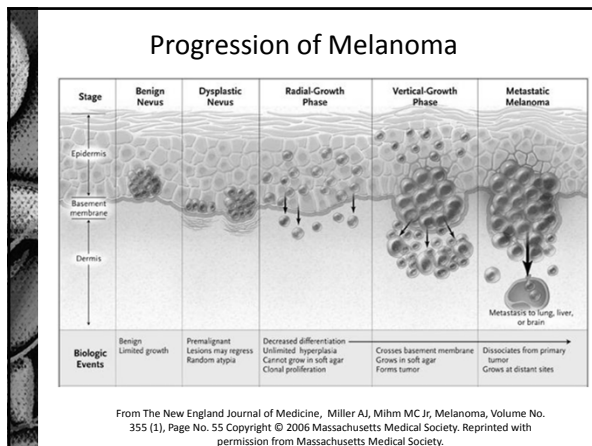
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See page 32 for enlarged view

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### Patient Presentation

- Median Age of diagnosis 45-55 years
- Diagnosis at presentation
  - 82-85% present with localized disease
  - 10-13% regional disease
  - 2-5% with metastatic disease

Miller AJ et al. *N Engl J Med.* 2006; 355: 51-65.

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### ABCDEs of Melanoma

	Benign	Malignant
<b>A</b> Symmetrical		Asymmetrical (the two sides do not match)
<b>B</b> Borders are even		Borders are uneven
<b>C</b> One color		Two or more colors
<b>D</b> Smaller than 1/4 inch		Larger than 1/4 inch
<b>E</b> Ordinary mole		Evolution of existing mole Changing in size, shape, color, or another trait

[www.skincancer.org](http://www.skincancer.org) accessed 2014 October 30 2014.

See page 32 for enlarged view

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## Biopsy

- Indicated for a suspicious lesion
- Full thickness excisional biopsy with 1-3mm margins into normal skin
  - Not always feasible (i.e. face, feet, large lesions)
  - Full thickness incisional biopsy or punch

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## Further Work Up

- History and physical exam
- Further dermatologic examination indicating other lesions
- >1mm thick
  - Baseline CXR and LFTs
- Lactate dehydrogenase (LDH)
- Suspected lymph node involvement confirmation

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## Lymph Node Involvement

- Important prognostic factor
- Complete lymph node dissection
  - Labor intensive
  - Unable to stain every section of node and may miss area showing metastasis
- Only 20% of patients with an intermediate thickness → regional nodal involvement
  - 80% are at risk for a bad outcome from the complete dissection of the LN
- Sentinel LN = First node that melanoma spreads to
  - Melanoma follows an orderly nodal distribution

Morton DL et al. *Ann Surg.* 2005; 242: 302-313.

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## Clark Level

- How deep the tumor has penetrated base histology
- Directly related to risk of metastasis to nodes
- Level I-V
  - Level I is restricted to epidermis (in situ)
  - Level V is metastatic

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## Breslow Thickness

- Similar to Clark level but uses a micrometer to measure tumor invasion through a microscope
- 0.75 mm (Clark Level II)
- > 0.75 - 1.5 mm (Clark Level III)
- > 1.5 - 4.0 mm (Clark Level IV)
- > 4.0 mm (Clark Level V)

[http://training.seer.cancer.gov/module\\_staging\\_cancer/unit03\\_sec04\\_part05\\_melanoma.html](http://training.seer.cancer.gov/module_staging_cancer/unit03_sec04_part05_melanoma.html)

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## Staging and 5 Year Survival Rates

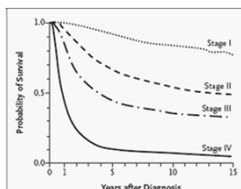


Figure 2. Relationship between the Stage of Melanoma and Survival.  
Kaplan-Meier survival curves are adapted from the American Joint Committee on Cancer.<sup>23</sup>

Stage I	<ul style="list-style-type: none"> <li>• A: &lt; 1 mm thick, no ulceration, Clark II-III</li> <li>• B: &lt; 1 mm thick with ulceration, Clark IV-V</li> <li>• 5yr OS: 90-95%</li> </ul>
Stage II	<ul style="list-style-type: none"> <li>• &gt; 1 mm thick with any characteristic</li> <li>• 5yr OS: 45-78%</li> </ul>
Stage III	<ul style="list-style-type: none"> <li>• Lymph node involvement</li> <li>• 5yr OS: 28-70% (depends on # of nodes)</li> </ul>
Stage IV	<ul style="list-style-type: none"> <li>• Metastatic Disease</li> <li>• 5yr OS: 18% (though may be increasing)</li> </ul>

From The New England Journal of Medicine, Tsao H, Atkins MB, Sober AJ, Management of Cutaneous melanoma, Volume No. 351(10), Page No. 1002 Copyright © 2004 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.  
American Cancer Society; <http://www.cancer.org/cancer/skin-cancer-melanoma/detailedguide/melanoma-skin-cancer-survival-rates>

See page 33 for enlarged view

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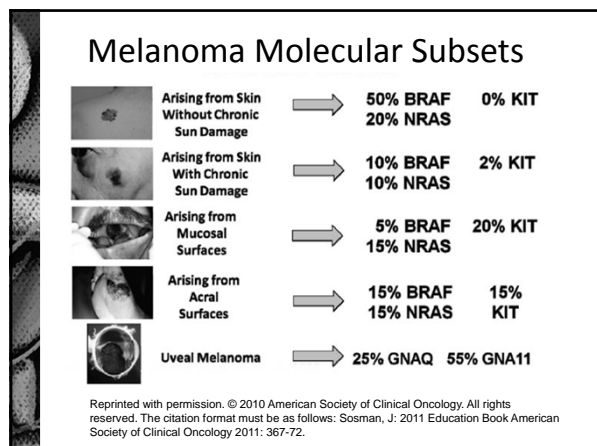
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## CE IN THE MIDDAY

### Immunotherapy and Targeted Treatment and Future of Melanoma Treatment

Christine M. Walko, Pharm.D., BCOP, FCCP, *Activity Chair*  
and  
R. Donald Harvey, Pharm.D., FCCP, BCOP

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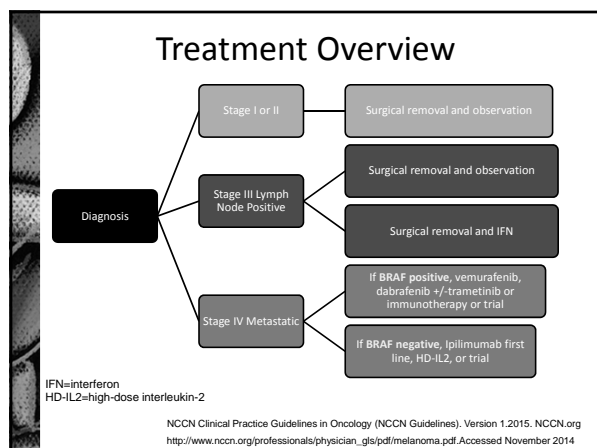
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## Cancer and Immune Evasion

- 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

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## General Immunotherapy Approaches

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

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## 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 2014

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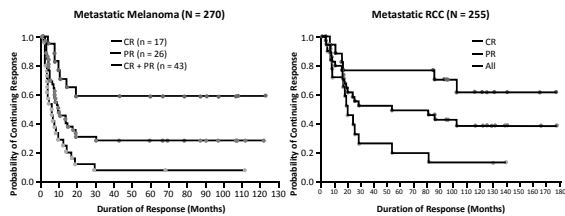
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## HD IL-2 Therapy: Durable Responses

- HD IL-2 produces durable responses in 6% to 10% of patients with advanced melanoma or renal cell carcinoma (RCC)
- Few relapses in patients responding for over 2.5 years (therefore, can be considered cured)
- FDA approval in 1992 (RCC) and 1997 (melanoma)



Atkins MB, et al. *J Clin Oncol*. 1999;17:2105-2116.  
McDermott DF, et al. *Expert Opin Biol Ther*. 2004;4:455-468.

## HD IL-2 Therapy in Melanoma and RCC

- High-dose IL-2 benefits patients, but:
  - Toxic
  - Impractical: must be delivered as an inpatient
- Use remains limited to selected patients treated at experienced centers
- Efforts to develop more tolerable IL-2 based regimens unsuccessful
- Efforts to better select patients who might benefit from HD IL-2 therapy have produced modest advances
- Proof of principle that immunotherapy can produce durable benefit in patients with solid tumor malignancies

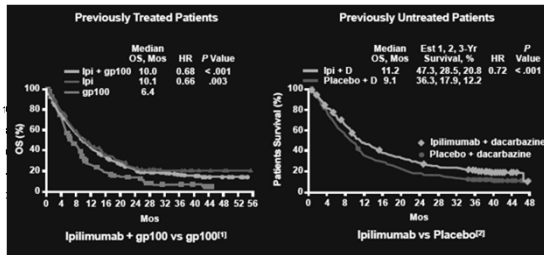
## Comparison of CTLA-4 vs PD-1

CTLA-4 pathway	PD-1 pathway
Exclusively on T cells	On T, B, and NK cells
Ligands: CD80 and CD86	Ligands: PD-L1 and PD-L2
Ligands only expressed on APCs	Ligand expressed on APCs and tumor cells
CTLA-4-deficient mice suffer early, fatal autoimmune syndrome	PD-1-deficient mice develop strain-specific autoimmunity late in life
Blockade enhances proliferation of CD4+ and CD8+ T cells with increase in ratio to regulatory T cells	Blockade enhances CD8+ T cells greater than CD4+ with increase of CD8+ to Tregs and cytotoxicity of CD8+

APC=antigen presenting cells

Greenwald RJ et al. *Ann Rev Immunol*. 2005;23:515-548. Chambers CA et al. *Ann Rev Immunol*. 2001;19:565-594. Dong H et al. *Nat Med*. 2002;8:793-800. Curran MA et al. *Proc Natl Acad Sci U S A*. 2010;107:4275-4280. Pilon-Thomas S et al. *J Immunol*. 2010;184:3442-3449.

## 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+ stools/day; start methylprednisone, 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 AST/ALT > 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 steroidal eye drops

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

## Ipilimumab Adverse Effects

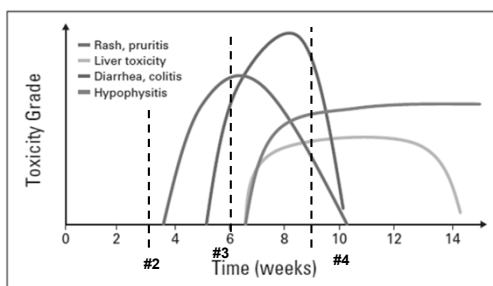
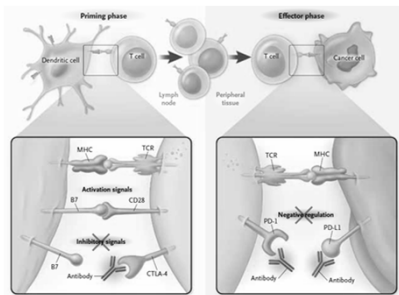


Fig 2. Kinetics of appearance of immune-related adverse event.

Reprinted with permission. © 2012 American Society of Clinical Oncology. All rights reserved.  
Weber JS et al. *J Clin Oncol*. 2012; 30:2691-7.

## The Role of Programmed Death Protein-1 (PD-1)



From The New England Journal of Medicine, Ribas A, Tumor Immunotherapy Directed at PD-1, Volume No. 366, Page No. 2518 Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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## 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

BMS-936558

### 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 Eng J Med.* 2012;366:2443-54.

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## 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 Eng J Med.* 2012;366:2443-54.

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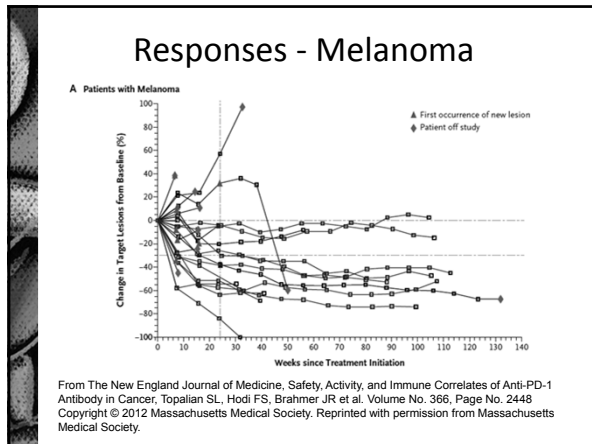
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### Selected Toxicity

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 Eng J Med.* 2012;366:2443-54.

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

Target	Antibody	Molecule	Development Stage
PD-1	Nivolumab (BMS-936558)	Fully human IgG4	Phase III multiple tumors
	Pembrolizumab (MK-3475)	Humanized IgG4	Approved
	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

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

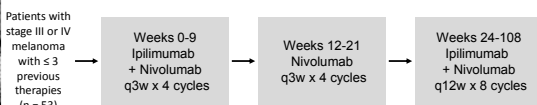
Agent	Pts, n	ORR (at Optimal Dose), %	Grades 3/4 Tx-Related AEs, %	6-Mo PFS, %	12-Mo PFS, %	Median PFS, Mos	1-Yr OS, %	2-Yr OS, %
Nivolumab (anti-PD-1) <sup>[1-3]</sup>	104	31 (41)	22	41	36	3.7	62	43
Pembrolizumab (anti-PD-1) <sup>[4,5]</sup>	135	38 (52)	13	NA	NA	> 7	81	NA
BMS 936559 (anti-PD-L1) <sup>[6]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

1. Topalian SL et al. *J Clin Oncol*. 2014;32:1020-1030. 2. Sznol M et al. ASCO 2013. Abstract 9006.  
3. Topalian SL et al. *N Engl J Med*. 2012;366:2443-2454. 4. Ribas A et al. ASCO 2013. Abstract 9009.  
5. Hamid O et al. *N Engl J Med*. 2013;369:134-144. 6. Brahmer JR et al. *N Engl J Med*. 2012. 366:2455-2465. 7. Hamid O et al. ASCO 2013. Abstract 9010.

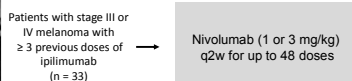
## Nivolumab + Ipilimumab: Phase I Study

- Concurrent therapy study design:



Escalating doses of nivolumab (0.3-10 mg/kg) and ipilimumab (1-10 mg/kg)

- 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: Efficacy

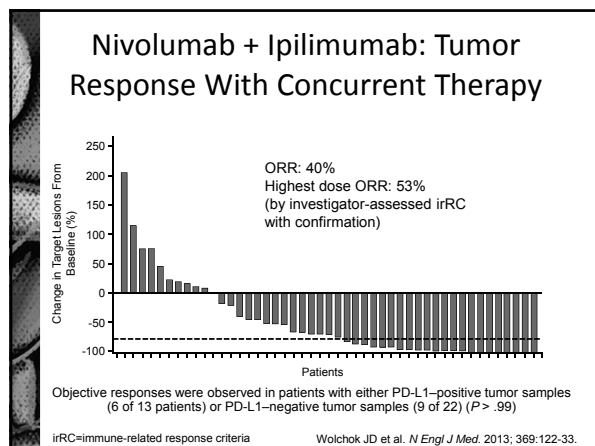
### Clinical activity in concurrent regimen

Cohort	Nivolumab + Ipilimumab, mg/kg	Response Evaluable Patients, n	CR, n	PR, n	ORR, %	≥ 80% Tumor Reduction at 12 W, n (%)
1	0.3 + 3	14	1	2	21	4 (29)
2	1 + 3	17	3	6	53	7 (41)
2a	3 + 1	15	1	5	40	5 (33)
3	3 + 3	6	0	3	50	0
All	-	52	5	16	40	16 (31)

### Clinical activity in sequenced regimen (n = 30)

- ORR: 20% (1 CR, 5 PR)
- 4 patients had ≥ 80% tumor reduction at first scheduled 8-wk tumor assessment

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




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### 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.

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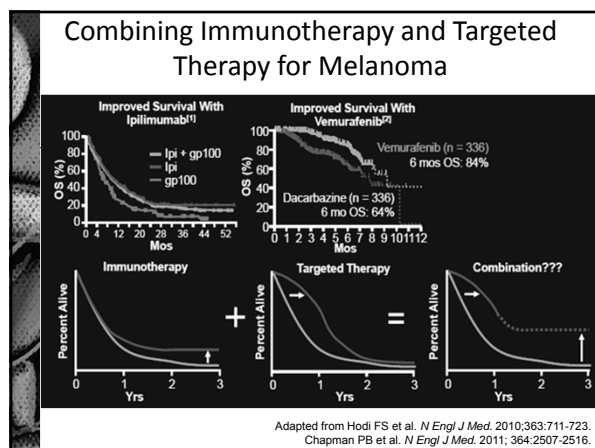
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## Ipilimumab + Vemurafenib Liver Toxicities in Phase I Testing

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 <sup>†</sup>	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 <sup>‡</sup>					
10	1	15	Vem discontinued for 7 days then restarted with dose reduction; ipi permanently discontinued (1 dose)	10	NA
16 <sup>§</sup>	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.

<sup>†</sup>Patient also had grade 2 increase in total bilirubin.

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

<sup>§</sup>Patient also had grade 3 increase in total bilirubin.

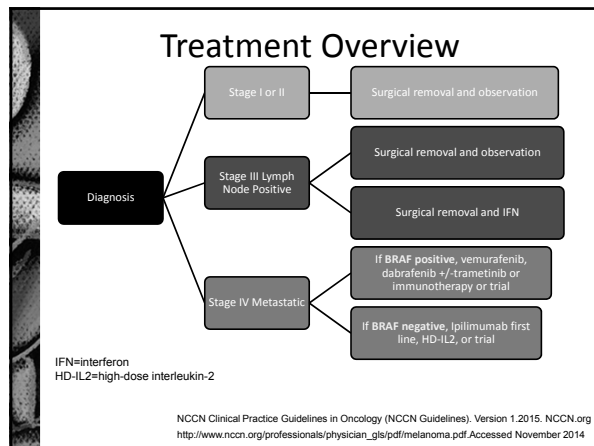
Ribas A et al. *N Engl J Med*. 2013;368:1365-1366.

Which of the following is true regarding single agent immunotherapy in melanoma?

- High response rates are commonly seen, but are of short duration
- All produce low response rates of short duration
- Long-term responses can be seen, but are in less than 20% of patients
- Responses are seen in over 50% and are very durable

Adverse events seen with ipilimumab and PD-1 antagonism include:

- Rash, cardiotoxicity, and myelosuppression
- Rash, hepatotoxicity, and diarrhea
- Cardiotoxicity, hepatotoxicity, and myelosuppression
- Diarrhea, hepatotoxicity, and myelosuppression



See page 33 for enlarged view

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### BRAF Mutant Melanoma

- Found in 40-50% of cutaneous melanoma
  - Nearly 60% of melanoma in skin without chronic sun-induced damage
  - 80-90% are the V600E and 5-12% are V600K
  - Generally non-overlapping with other mutations
- Results in enhanced BRAF kinase activity and subsequent MAPK activation
- Current FDA approved therapies:
  - BRAF inhibitors: Vemurafenib and Dabrafenib
  - MEK inhibitor: Trametinib

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### Phase III Vemurafenib vs. Dacarbazine

**N = 675**

Previously untreated, unresectable Stage IIIC or IV melanoma with BRAF V600E mutations

R A N D O M I Z A T I O N

Vemurafenib 960 mg PO BID

Dacarbazine 1000 mg/m<sup>2</sup> IV every 3 weeks

- Co-primary endpoints:** Progression-free survival (PFS) and overall survival (OS)
- Secondary endpoints:** Response rate (RR), response duration and safety
- Stratification by stage, performance status, LDH level and geographic region
- Enrolled January 2010 to December 2010 in 12 countries

Chapman PB et al. *N Engl J Med*. 2011;364:2507-2516.

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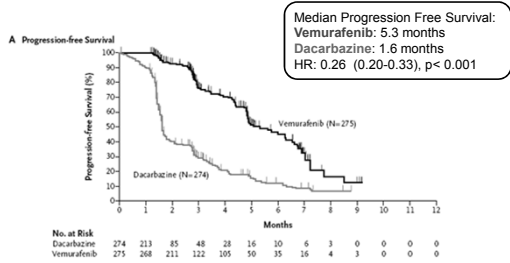
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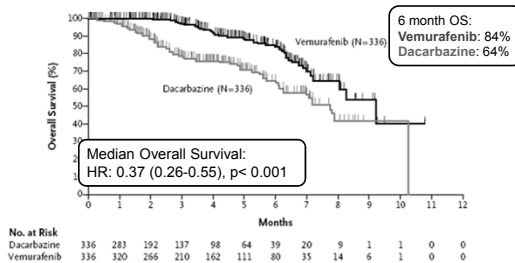


## Vemurafenib vs. Dacarbazine PFS



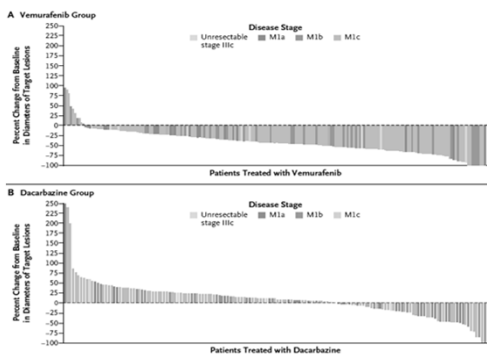
From The New England Journal of Medicine, Chapman PB, Hauschild A, Robert C et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation, Volume No. 364, Page No. 2512 Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

## Vemurafenib vs. Dacarbazine OS



From The New England Journal of Medicine, Chapman PB, Hauschild A, Robert C et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation, Volume No. 364, Page No. 2512 Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

## Vemurafenib vs. Dacarbazine RR



From The New England Journal of Medicine, Chapman PB, Hauschild A, Robert C et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation, Volume No. 364, Page No. 2513 Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

## Vemurafenib and Dacarbazine Toxicity

Toxicity	Vemurafenib		Dacarbazine	
	Grade 2	Grade 3	Grade 2	Grade 3
Arthralgia	18%	3%	< 1%	< 1%
Nausea	7%	1%	11%	2%
Fatigue	11%	2%	12%	2%
Diarrhea	5%	< 1%	1%	< 1%
Keratoacanthoma	2%	6%	0%	0%
Hyperkeratosis	5%	1%	0%	0%
Cutaneous SqCC	N/A	12%	N/A	< 1%

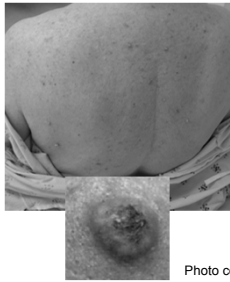
The majority of all toxicities were grade 2 or less.  
Most common events in the vemurafenib arm were cutaneous events, arthralgia and fatigue.

N/A = not applicable  
sqCC=squamous cell carcinoma

Chapman PB et al. *N Engl J Med.* 2011;364:2507-2516.

## BRAF Inhibitor Dermatologic Effects

Maculopapular rash with keratoacanthomas

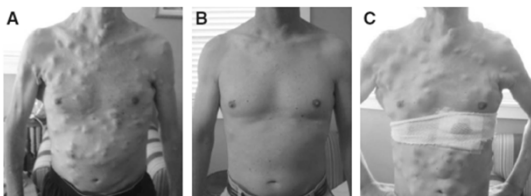


Pustular "white head" reactions treated like traditional acne



Photo courtesy of Dr. Walko, used with patient permission

## Vemurafenib Relapse

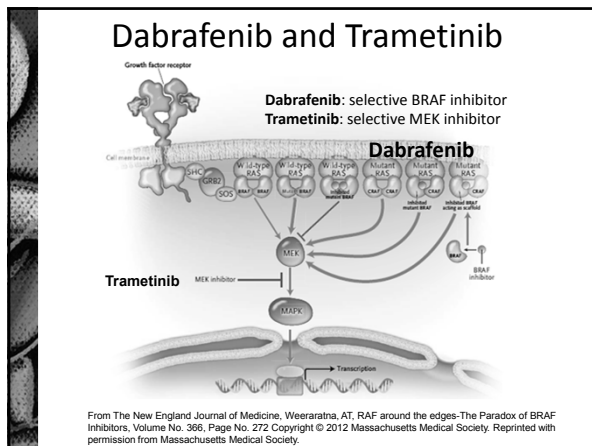


Baseline before therapy

15 weeks of therapy with vemurafenib

23 weeks of therapy with vemurafenib

Reprinted with permission. © 2011 American Society of Clinical Oncology. All rights reserved.  
Wagle N et al. *J Clin Oncol.* 2011; 29:3085-96.




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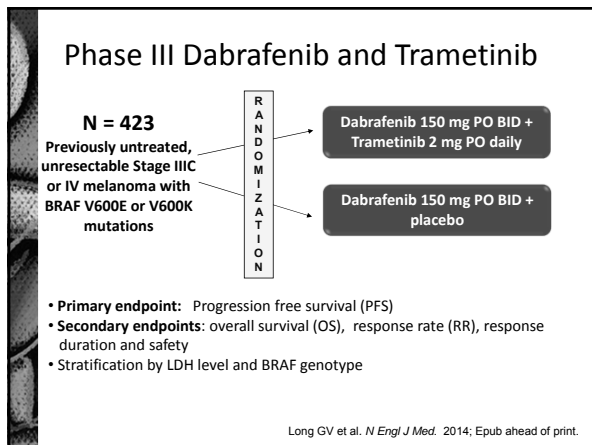
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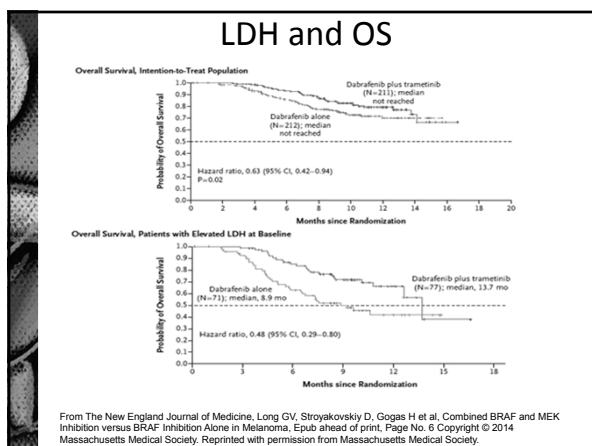
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## Phase III Dabrafenib and Trametinib

	Dabrafenib	Dabrafenib and Trametinib	HR	P value
Overall Population				
Median PFS	8.8	9.3	0.75	0.03
Median OS	NR	NR	0.63	0.02
Elevated LDH n = 148				
Median PFS	3.8	7.1	0.64	
Median OS	8.9	13.7	0.48	

\*All time expressed in months

Long GV et al. *N Eng J Med.* 2014; Epub ahead of print.

## Dabrafenib and Trametinib: Toxicity

Toxicity	Dabrafenib		Dabrafenib + Trametinib	
	All grade	Grade 3 and 4	All grade	Grade 3 and 4
Pyrexia	28%	2%	51%	6%
Rash	22%	1%	23%	0%
Peripheral Edema	5%	< 1%	14%	< 1%
Hand Foot Syndrome	27%	< 1%	5%	0%
Hyperkeratosis	32%	< 1%	3%	0%
Cutaneous SqCC	9%	4%	2%	2%

The majority of all toxicities were grade 2 or less.

SqCC=squamous cell carcinoma

Long GV et al. *N Eng J Med.* 2014; Epub ahead of print.

## Dabrafenib and Trametinib: Summary

- Resistance to BRAF inhibitors typically occurs after 6-7 months in most BRAF mutant metastatic melanoma patients
- Combination of a BRAF and MEK inhibitors may suppress downstream resistance mechanisms
  - Combination therapy had longer mPFS compared with monotherapy
  - Median overall survival not yet reached
- Combination therapy resulted in higher occurrence of pyrexia, chills, nausea and vomiting but less skin toxicities
- Potential place in therapy:
  - First line for BRAF positive metastatic melanoma

mPFS=median progression free survival

Flaherty KT et al. *N Eng J Med.* 2012; 367:1694-703.

### Patient Case

- WK is a 38 yo female who was initially diagnosed with stage IIIC melanoma of the neck
  - Modified radical neck dissection
  - 2 months of adjuvant interferon before stopping due to toxicity
- PET scan at 6 months shows numerous sites compatible with metastatic disease
- Pathology notable for the 1799 T>A (V600E) mutation in the BRAF gene
- She is willing to travel for a clinical trial.

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What therapy would be most beneficial for this patient?



- a. Single agent trametinib
- b. Single agent vemurafenib
- c. Combination dabrafenib and trametinib
- d. Combination vemurafenib and dabrafenib

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Compared to a BRAF inhibitor alone, which toxicity is LESS likely with combination BRAF + MEK inhibition?



- a. Pyrexia
- b. Rash
- c. Peripheral edema
- d. Squamous cell carcinoma

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## Future Challenges and Directions

- Optimal sequencing of therapy for BRAF-positive patients
- Optimal use of PD-1 or PD-L1 inhibitors
  - Sequential therapy
  - Combination immunotherapy
  - Combination with BRAF inhibitors
- Managing drug resistance
  - Genetic tumor profiling

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## Genetic Assessment: Patient Case

- 71 yo man diagnosed with metastatic melanoma in April 2013 when he presented with a lesion on the left chin and also had nodal involvement.
- Treatment Hx
  - Surgical resection of primary site and lymphadenectomy
  - Ipilimumab x 3 doses 11/2013 – complicated by ipilimumab -induced colitis requiring high-dose steroids and infliximab
  - Radiation therapy to the neck area and left lung from 11/2013 -1/2014
  - CT scan in July 2014 demonstrated recurrent disease
- Somatic genetic analysis:
  - Lymph node from 08/11/2014
- Clinical Question
  - Future treatment options

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## Somatic Genetic Analysis

Gene	Variant	Notes
NRAS	Amplification	<ul style="list-style-type: none"> <li>• NRAS activating mutations have been reported to activate the RAF/MEK/ERK and PI3K pathways leading to hyperactivation of CDK4/6.</li> <li>• Numerous clinical trials available targeting this pathway with various combinations of inhibitors</li> </ul>
CDK4	Amplification	<ul style="list-style-type: none"> <li>• Amplification of CDK4 may lead to excessive protein expression and activity, resulting in unrestricted cell cycle progression.</li> <li>• Several CDK4/6 inhibitors are currently being studied in clinical trials</li> </ul>
MDM2	amplification	<ul style="list-style-type: none"> <li>• This gene encodes a nuclear-localized E3 ubiquitin ligase and regulates the tumor suppressor p53. Controls entry into S-phase and ultimately mitosis</li> <li>• Putative amplification of MDM2 has been reported in 4% of cases in the Skin Cutaneous Melanoma TCGA dataset.</li> <li>• Phase I clinical trial with MDM2 inhibitor currently enrolling</li> </ul>

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## Potential Trial Considerations

NCT ID	Title	Target	Compound
NCT01781572	A Phase Ib/II, Multicenter, Open Label, Study of LEE011 in Combination With MEK162 in Adult Patients With NRAS Mutant Melanoma	MEK, CDK4/6	LEE011 and MEK162
NCT01449058	A Phase Ib Study of MEK162 Plus BYL719 in Adult Patients With Selected Advanced Solid Tumors	MEK, PI3K	BYL719 and MEK162
NCT02187783	Modular Phase II Study to Link Targeted Therapy to Patients With Pathway Activated Tumors: Module 8 - LEE011 for Patients With CDK4/6 Pathway Activated Tumors	CDK4/6	LEE011
NCT02065063	A Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Anti-Cancer Activity of Trametinib in Combination With Palbociclib in Subjects With Solid Tumors	MEK, CDK4/6	Trametinib Palbociclib

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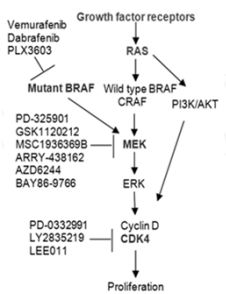
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## Actionable Discussion:

Which clinical trial option targeting this pathway would be best given NRAS and CDK4 amplification?



Jianli Dong (2013). Overcoming Resistance to BRAF and MEK Inhibitors by Simultaneous Suppression of CDK4. Melanoma - From Early Detection to Treatment, Dr. H. Duc (Ed.), ISBN: 978-953-51-0961-7, InTech, DOI: 10.5772/53820. Available from: <http://www.intechopen.com/books/melanoma-from-early-detection-to-treatment/overcoming-resistance-to-braf-and-mek-inhibitors-by-simultaneous-suppression-of-cdk4>

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## Conclusions

- Genetic testing is a standard part of the metastatic melanoma work up
  - BRAF V600E or K positive patients are eligible for treatment with BRAF-inhibitors with or without MEK-inhibitor directed therapy
  - Patients lacking the BRAF mutation should be directed towards immunotherapy with HD-IL2, ipilimumab or pembrolizumab
- Novel targeted and immunotherapy agents have unique side effect profiles that provide opportunities for pharmacists in terms of patient education and supportive care
- Ongoing clinical trials are aimed at addressing optimal sequencing and combinations of therapy for both BRAF-positive and negative patients.

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## Progression of Melanoma

Stage	Benign Nevus	Dysplastic Nevus	Radial-Growth Phase	Vertical-Growth Phase	Metastatic Melanoma
<b>Biologic Events</b>	Benign Limited growth	Premalignant Lesions may regress Random atypia	Decreased differentiation Unlimited hyperplasia Cannot grow in soft agar Clonal proliferation	Crosses basement membrane Grows in soft agar Forms tumor	Dissociates from primary tumor Grows at distant sites

From The New England Journal of Medicine, Miller AJ, Mihm MC Jr, Melanoma, Volume No. 355 (1), Page No. 55 Copyright © 2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

## ABCDEs of Melanoma

		Benign	Malignant	
<b>A</b>	Symmetrical			Asymmetrical (the two sides do not match)
<b>B</b>	Borders are even			Borders are uneven
<b>C</b>	One color			Two or more colors
<b>D</b>	Smaller than 1/4 inch			Larger than 1/4 inch
<b>E</b>	Ordinary mole			Evolution of existing mole Changing in size, shape, color, or another trait

[www.skincancer.org](http://www.skincancer.org) accessed 2014 October 30 2014.



## Staging and 5 Year Survival Rates

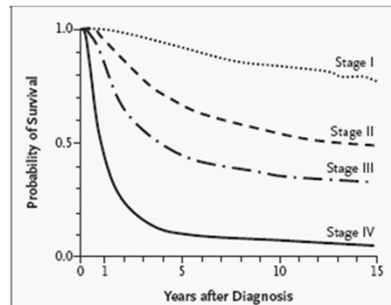


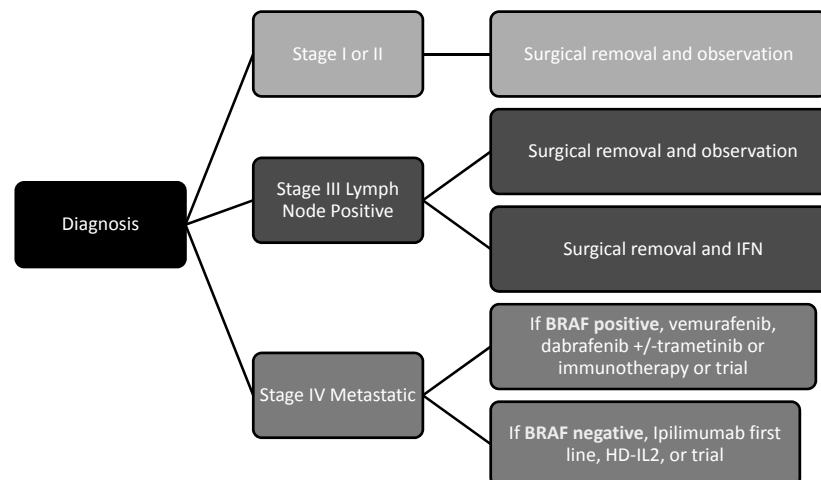
Figure 2. Relationship between the Stage of Melanoma and Survival.

Kaplan-Meier survival curves are adapted from the American Joint Committee on Cancer.<sup>23</sup>

Stage I	<ul style="list-style-type: none"> <li>A: &lt; 1mm thick, no ulceration, Clark II-III</li> <li>B: &lt; 1 mm thick with ulceration, Clark IV-V</li> <li>5yr OS: 90-95%</li> </ul>
Stage II	<ul style="list-style-type: none"> <li>&gt; 1 mm thick with any characteristic</li> <li>5yr OS: 45-78%</li> </ul>
Stage III	<ul style="list-style-type: none"> <li>Lymph node involvement</li> <li>5yr OS: 28-70% (depends on # of nodes)</li> </ul>
Stage IV	<ul style="list-style-type: none"> <li>Metastatic Disease</li> <li>5yr OS: 18% (though may be increasing)</li> </ul>

From The New England Journal of Medicine, Tsao H, Atkins MB, Sober AJ, Management of Cutaneous melanoma, Volume No. 351(10), Page No. 1002 Copyright © 2004 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. American Cancer Society; <http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-survival-rates>

## Treatment Overview



IFN=interferon  
HD-IL2=high-dose interleukin-2

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 1.2015. NCCN.org  
[http://www.nccn.org/professionals/physician\\_gls/pdf/melanoma.pdf](http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf). Accessed November 2014