MELANOMA UPDATE

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Disclosure

I do not have any relevant financial relationships with any commercial interests
Learning Objectives

- Describe treatment options for a patient with metastatic melanoma
- Identify a patient that is a candidate for vemurafenib, dabrafenib and trametinib
- Explain the benefits and disadvantages of ipilimumab, pembrolizumab and nivolumab in the treatment of metastatic melanoma
- Recognize the toxicities of ipilimumab, pembrolizumab and nivolumab and discuss strategies for management
Epidemiology

- Skin cancer is most common cancer in US
- Melanoma accounts for ~2% of all skin cancers
- 73,870 estimated new cases of melanoma in US in 2015
- 9,940 est. deaths from melanoma in 2015
- 2,230 est. new cases in Virginia in 2015
- Incidence continues to increase (~2.8%/yr)
- Median age at diagnosis is 59
Melanoma Risk Factors

- Personal or family history
- Atypical or numerous moles (>50)
- Sun sensitivity
- Fair skin, light hair, freckling, green/blue eyes
- Excessive sun exposure, including sunburns
- Tanning booths
- Immunusuppression (drug or disease induced)
- History of basal or squamous cell skin cancer
Approximately 85% of melanoma cases can be attributed to UV radiation!
Melanoma Prevention

- Avoid intense sun exposure, especially mid-day
- Wear protective clothing, hats
- Wear sunscreen with SPF >15 on exposed skin & reapply at least every 2 hours
- Wear sunglasses
- Avoid sunbathing/tanning

**Especially important for children**
ABCs of Melanoma

- Asymmetry
- Border irregularity
- Color variation
- Diameter >6 mm
- Evolving over time

http://en.wikipedia.org/wiki/Melanoma
Prognosis

- Breslow depth
- Clark’s level
- Ulceration
- Mitotic rate
Treatment

- Stage IA: surgery alone
- Stage IB and IIA: surgery +/- clinical trial or obs
- Stage IIB and IIC: surgery +/- clinical trial, obs or high-dose interferon (HDI)
- Stage III: surgery +/- clinical trial, obs, HDI or PEG-interferon
- Stage IV: chemo, interleukin-2 (IL-2), ipilimumab, pembrolizumab, nivolumab, vemurafenib, dabrafenib, trametinib

History of Melanoma Treatment

- 1975 DTIC
- 1996 IFN-α2b
- 1998 IL-2
- Mar 2011 Ipilimumab, PEG-IFN
- May 2013 Dabrafenib, Trametinib
- Aug 2011 Vemurafenib
- September 2014 Pembrolizumab
- December 2014 Nivolumab
Dacarbazine (DTIC)

- Alkyating agent
- Objective response rate: 5-12%
- Responses usually transient (1-2% long-term response)
- Median overall survival: 6-7 months
- Most common AEs: n/v, pain, constipation, myelosuppression
High-Dose Aldesleukin (IL-2)

- T- & B-cell proliferation, stimulates immune system
- 600,000 U/kg IV q8h x 14 doses, repeated after 9 days rest (28 doses total)
- Objective response rate: ~15%
  - 5% of patients achieve long-term CR
  - No benefit in OS
  - No phase III data
- Requires treatment in intensive setting
IL-2 Toxicities

- Capillary leak: hypotension, edema, wt gain
- Cardiac: SVT, CHF, arrhythmias
- Neuro: confusion, somnolence, anxiety
- GI: nausea, vomiting, diarrhea
- Resp: dyspnea, pulmonary infiltrates
- Infection
- Renal (oliguria), hepatic (incr Bili)
- Fever, chills
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September 2014 Pembrolizumab

Nivolumab December 2014

www.fda.gov
BRAF and MEK Inhibition

- 50% melanomas have BRAF V600E or V600K mutations
- Mutation causes cell proliferation
- Part of the MAP kinase pathway
  - BRAF inhibition (BRAFi)
  - MEK inhibition
# BRAF Inhibitors

<table>
<thead>
<tr>
<th>Vemurafenib</th>
<th>Dabrafenib</th>
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<tbody>
<tr>
<td>960 mg PO twice daily, without food</td>
<td>150 mg PO every 12 hours, without food</td>
</tr>
<tr>
<td>-CYP3A4 substrate and inducer</td>
<td>-Substrate of CYP2C8 and 3A4</td>
</tr>
<tr>
<td>-Moderate 1A2 inhibitor</td>
<td>-Moderate inducer of 2B6, 2C19, 2C8, 2C9, 3A4</td>
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<tr>
<td>Arthralgia, rash, photosensitivity, fatigue, cutaneous squamous cell carcinoma, nausea, ↑LFTs</td>
<td>-Avoid drugs that ↑ gastric pH</td>
</tr>
<tr>
<td></td>
<td>Hyperkeratosis, papilloma, headache, fever, arthralgia, hand-foot syndrome, hyperglycemia, G6PD deficiency</td>
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Vemurafenib Study

Untreated, unresectable stage IIIC or metastatic, +BRAF V600E mutation

Vemurafenib 960mg PO BID (n=336)

Interim analysis: improved OS and PFS for vemurafenib. DTIC pts able to receive vemurafenib

6 mo OS: 84%
Obj response: 48%*

DTIC 1g/m² q3w (n=336)

6 mo OS: 64%
Obj response: 5%

*p <0.05

Trametinib

- Selective inhibitor of MEK1 and MEK2
- Patients with V600E or V600K mutations not previously treated with a BRAF inhibitor
  - Single agent or with dabrafenib
- 2 mg once daily, without food
- Skin toxicity, cardiomyopathy (monitor LVEF), pneumonitis, ocular toxicity, ↑ liver enzymes
- Overall response rate (single agent): 22%
Activated MAP kinase pathway signaling

Inactive MAP kinase pathway

Constitutively activated MAP kinase pathway in the setting of BRAF mutation

NRAS  BRAF  MEK  ERK

NRAS  BRAF  MEK  ERK

Dabrafenib + Trametinib vs Vemurafenib Study

Untreated, unresectable stage IIIC or metastatic, +BRAF V600E/K mutation

Dabrafenib 150mg PO BID +Trametinib 2mg PO QD (n=352)
- 1 yr OS: 72%*
- Obj response: 64%*
- Cutaneous SCC: 1%
- Fever 53%

Vemurafenib 960mg PO BID + Placebo (n=352)
- 1 yr OS: 65%
- Obj response: 51%
- Cutaneous SCC: 18%
- Rash 43%

*p <0.05

Immune Checkpoints

- Negative immune regulators
- Help maintain immune homeostasis
- Upregulate in response to T cell activation
- Turn off immune system
- Located on T cells
- Immune checkpoint inhibition → immune stimulation
  - Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4)
  - Programmed Death 1 (PD-1)
Immune Checkpoints

Ipilimumab

- Fully human monoclonal antibody
  - CTLA-4 inhibitor
  - T-lymphocyte proliferation and IL-2 production
- Unresectable or metastatic melanoma, 1\textsuperscript{st} line
- Risk Evaluation and Mitigation Strategy (REMS) program
- 3mg/kg IV over 90 min via low-protein binding filter (LPBF) every 3 wks x 4 doses (may repeat)
- May give maintenance every 12 weeks
Ipilimumab + Vaccine Study

Previously treated unresectable stage III or metastatic

Ipilimumab 3 mg/kg + gp 100 peptide vaccine (n=403)
- Median OS: 10 mo*
- Obj response: 5.7%
- 2 yr survival: 21.6%

Ipilimumab 3 mg/kg + placebo (n=137)
- Median OS: 10.1 mo*
- Obj response: 10.9%
- 2 yr survival: 23.5%

gp 100 peptide vaccine + placebo (n=136)
- Median OS: 6.4 mo
- Obj response: 1.5%
- 2 yr survival: 13.7%

*p <0.05

**Ipilimumab +DTIC Study**

Previously untreated metastatic melanoma

- **Ipilimumab 10 mg/kg + DTIC 850 mg/m² q3w x4, then DTIC q3w x 4 (n=250)**
  - Ipilimumab or placebo q12 wks (n=43)
  - Median OS: 11.2 mo*
  - Obj response: 15.2%
  - 2 yr survival: 28.5%
  - 5 yr survival: 18.2%

- **DTIC 850 mg/m² + placebo q3w x4, then DTIC q3w x 4 (n=252)**
  - Ipilimumab or placebo q12 wks (n=53)
  - Median OS: 9.1 mo
  - Obj response: 10.3%
  - 2 yr survival: 17.9%
  - 5 yr survival: 8.8%

*p <0.05

IMMUNE-MEDIATED ADVERSE REACTIONS
Follow color code to appropriate management guide section.

GASTROINTESTINAL
GO TO PAGE 6
Signs and symptoms such as
• Diarrhea
• Abdominal pain
• Blood or mucus in stool
• Bowel perforation
• Peritoneal signs
• Ileus

NEUROLOGIC
GO TO PAGE 12
Symptoms such as
• Unilateral or bilateral weakness
• Sensory alterations
• Paresthesia

LIVER
GO TO PAGE 8
Signs such as
• Abnormal liver function tests (eg, AST, ALT) or total bilirubin

ENDOCRINE
GO TO PAGE 14
Signs and symptoms such as
• Fatigue
• Headache
• Mental status changes
• Abdominal pain
• Unusual bowel habits
• Hypotension
• Abnormal thyroid function tests and/or serum chemistries

SKIN
GO TO PAGE 10
Symptoms such as
• Pruritus
• Rash

OTHER ADVERSE REACTIONS, including ocular manifestations
GO TO PAGE 16

Please see each organ system section for related guidance.

Ipilimumab AE Management

**Determine Severity of Enterocolitis**

**Grade 2 toxicity**

**Moderate**
- 4 to 6 stools/day over baseline
- Abdominal pain
- Blood or mucus in stool

**Management**
- Withhold YERVOY
  - Administer antidiarrheal treatment while etiology is investigated

**FOLLOW-UP**
- Symptoms Resolved
  - Resume YERVOY if symptoms have improved to mild severity or resolution
- Symptoms Ongoing >1 week
  - Start systemic corticosteroids (e.g., 0.5 mg/kg/day of prednisone or equivalent)
  - Continue steroids until improvement to mild severity or resolution; taper steroids as medically appropriate
  - Resume YERVOY if symptoms have improved to at least mild severity, and steroid dose is 7.5 mg prednisone equivalent or less
  - IF SYMPTOMS WORSEN TO SEVERE, SEE BELOW

**Grade 3-4 toxicity**

**Severe or Life Threatening**
- ≥ 7 stools/day over baseline
- Peritoneal signs consistent with bowel perforation
- Ileus
- Fever

**Management**
- Permanently Discontinue YERVOY
  - Rule out bowel perforation; if bowel perforation is present, do not administer corticosteroids
  - Consider endoscopic evaluation
  - Administer systemic corticosteroids of 1 to 2 mg/kg/day of prednisone or equivalent

**FOLLOW-UP**
- Symptoms Resolved
  - Continue steroids until improvement to mild and taper steroids over 1 month
- Symptoms Ongoing
  - Patient should be continually evaluated for evidence of gastrointestinal perforation or peritonitis
  - Consider repeat endoscopy
  - Consider alternative immunosuppressive therapy

Pembrolizumab

- Humanized monoclonal antibody
  - Blocks interaction between PD-1 and its ligands, PD-L1 and PD-L2
  - Increased tumor-specific T-cell activity
- Unresectable or metastatic melanoma after ipilimumab and (if BRAF +) BRAF inhibitor
- 2 mg/kg IV over 30 minutes via LPBF every 3 wks until progression
Anti-PD-1
Pembrolizumab study (Phase I)

Metastatic melanoma, ipilimumab-refractory

Pembrolizumab 2 mg/kg q3w until progression (n=89)

- Obj response: 26%

Pembrolizumab 10 mg/kg q3w until progression (n=84)

- Obj response: 26%

AEs: Fatigue, pruritis, rash; ~14% immune-mediated

Pembrolizumab

May see in first-line setting due to high rate of response

Phase III data coming soon
Nivolumab

- Fully human monoclonal antibody
  - Blocks interaction between PD-1 and its ligands, PD-L1 and PD-L2
  - Increased tumor-specific T-cell activity
- Unresectable or metastatic melanoma after ipilimumab and (if BRAF +) BRAF inhibitor
- 3 mg/kg IV over 60 minutes via LPBF every 2 weeks until disease progression
Nivolumab vs DTIC Study

Previously untreated metastatic melanoma

Nivolumab 3 mg/kg q2w + placebo (n=210)
- Median OS: not reached*
- Obj response: 40%*
- 1 yr survival: 72.9%*

DTIC 1000 mg/m² q3w + placebo (n=208)
- Median OS: 10.8 mo
- Obj response: 13.9%
- 1 yr survival: 42.1%

Nivolumab AEs: Fatigue, pruritis, diarrhea; ~8% immune-mediated

*p <0.05

Nivolumab

Will see in first-line setting due to high rate of response & quality of data
## Immune checkpoint inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-mediated AEs</td>
<td>60%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>4%</td>
</tr>
<tr>
<td>GI (Diarrhea, colitis)</td>
<td>33%^</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>Endocrine^</td>
<td>15%</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Hepatic (↑ AST/ALT)</td>
<td>8%^</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Dermatologic (Rash)</td>
<td>40%^</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40%</td>
<td>47%</td>
<td>25%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1%</td>
<td>4%</td>
<td>5%</td>
</tr>
</tbody>
</table>

| First-line, FDA          | Yes        | No            | No        |
| First-line, clinically   | Yes        | Maybe         | Yes       |

^primarily immune mediated
Approx Cost of Treating Melanoma

- Dacarbazine 1g/m² x 2 cycles: $440
- High dose IL-2 x 28 doses: $72,000
- Ipilimumab 3mg/kg x 4 doses: $120,000
- Pembrolizumab x 6 mo: $75,000
- Nivolumab x 6 mo: $75,000
- Vemurafenib x 6 mo: $56,000
- Dabrafenib x 6 mo: $46,000
- Trametinib x 6 mo: $52,000
Summary

- Risk factors
- Prevention: limit sun exposure
- Recommend sunscreen, educate on proper use
- Early detection = cure. Remember ABCs
- New treatments promising, but toxic & costly
- Recommend clinical trials when available
<table>
<thead>
<tr>
<th>Drug</th>
<th>OR</th>
<th>CR</th>
<th>Duration</th>
<th>OS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dacarbazine</td>
<td>5-15%</td>
<td>5%</td>
<td>3-6 mo</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>High dose IL-2</td>
<td>~15%</td>
<td>~5%</td>
<td>Years</td>
<td>No</td>
<td>High toxicity</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>10-15%</td>
<td>~2%</td>
<td>5+ years</td>
<td>Yes</td>
<td>Immune mediated AEs. Slow time to respond</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>25%</td>
<td>~1%</td>
<td>Years?</td>
<td>?</td>
<td>After ipi/BRAFi, fewer immune AEs than ipi</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>40%</td>
<td>~8%</td>
<td>Years?</td>
<td>Yes</td>
<td>1st or 2nd line, fewer immune mediated AEs</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>48%</td>
<td>~2%</td>
<td>3-6 mo</td>
<td>Yes</td>
<td>BRAF V600E/K(+), rapid responses, skin toxicity</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trametinib</td>
<td>22%</td>
<td>~2%</td>
<td>3-6 mo</td>
<td>Yes</td>
<td>BRAF V600E/K(+), rapid responses, skin toxicity</td>
</tr>
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</table>

*When combined with dabrafenib

OR = Objective response, CR= complete response, OS= overall survival
Future of Melanoma Treatment

- www.clinicaltrials.gov, >1000 melanoma trials
- New CTLA-4 blockers
- New PD-1 inhibitors
- Signal transduction inhibitors
  - New BRAF and MEK inhibitors
  - P13K, CDK inhibitors
- Vaccines
- Adoptive cell therapy
- Combination treatment
  - Ipilimumab + Sargramostim (GM-CSF)
  - Ipilimumab + Nivolumab – 40% objective response
What Can You Do?

- Educate patients on risks and prevention
  - Focus on children
  - Avoid sunbathing and tanning booths
- Know expected toxicities
- Initiate early supportive care for patients experiencing adverse effects
- Evaluate patient’s drug regimens for interactions
- Inform patients & prescribers of clinical trials
BT is a 62 yom with a past medical history of hypertension and high cholesterol who was recently diagnosed with metastatic melanoma. Which of the following is the most effective first-line treatment option for BT?

A. Interleukin-2  
B. Interferon  
C. Dacarbazine  
D. Ipilimumab
A nurse comes to your pharmacy and asks what she needs to know about administering nivolumab for a patient with metastatic melanoma. Which of the following is correct?

A. Infuse over 4-6 hours
B. Premedicate with acetaminophen & diphenhydramine
C. Infuse via a low-protein binding filter
D. The dose is 2 mg/kg every 3 weeks
KN is a 48 yof with newly-diagnosed unresectable melanoma who comes to the pharmacy to pick up her prescriptions for trametinib and dabrafenib. Which of the following is an important counseling point for KN?

A. Check skin for new cutaneous squamous cell cancers
B. Immune-mediated adverse reactions are common
C. These agents are effective for BRAF-negative melanoma
D. Melanoma responds slowly to these agents
References


Dacarbazine

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Ipilimumab

- Ipilimumab (Yervoy™) Injection Prescribing Information. Bristol-Myers Squibb, March 2015

Pembrolizumab

- Pembrolizumab (Keytruda) Injection Prescribing Information. Merck & Co., Inc., January 2015
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