Updates on the Treatment of Metastatic Melanoma
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Conflicts of Interest
- Nothing to Disclose

Learning Objectives
- Describe the mechanisms of action of the new drugs that have been recently approved for the treatment of metastatic melanoma
- Identify the adverse effects associated with the drugs that have been recently approved for the treatment of metastatic melanoma
- Summarize the survival benefit of each of the newly approved agents for metastatic melanoma.

Outline
- Melanoma Definition/Epidemiology
- Melanoma Prognosis
- Melanoma Treatment (Historical)
- New Agents for Melanoma
  - Mechanism
  - Efficacy
  - Adverse Effects

Melanoma: Background & Epidemiology
- Melanoma is a cancer of pigment-producing cells, melanocytes
  - Can occur in the skin, eyes, and mucous membranes
  - 5th most common type of cancer in men; 6th most common type of cancer in women

<table>
<thead>
<tr>
<th>Year Estimates</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>73,870</td>
<td>9,940</td>
</tr>
<tr>
<td>Men</td>
<td>42,670</td>
<td>6,640</td>
</tr>
<tr>
<td>Women</td>
<td>31,200</td>
<td>3,300</td>
</tr>
</tbody>
</table>

Melanoma Epidemiology

- Melanoma incidence has been increasing about 1.8% per year for the past decade

![Melanoma Epidemiology Graph]

Melanoma Epidemiology

Percent of Cases by Stage

- Localized (84%)
- Confined to Primary Site
- Regional (9%) Spread to Regional Lymph Nodes
- Distant (4%) Cancer Has Metastasized
- Unknown (3%) Unstaged

![Melanoma Epidemiology Pie Chart]

Background: Melanoma Prognosis

<table>
<thead>
<tr>
<th>Survival by Stage</th>
<th>5 year survival (%)</th>
<th>10 year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>IB</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>IIA</td>
<td>86</td>
<td>67</td>
</tr>
<tr>
<td>IIB</td>
<td>79</td>
<td>57</td>
</tr>
<tr>
<td>IIBC</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>IIIA</td>
<td>78</td>
<td>68</td>
</tr>
<tr>
<td>IIIB</td>
<td>59</td>
<td>43</td>
</tr>
<tr>
<td>IIIBC</td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td>IV</td>
<td>19-20</td>
<td>5-15</td>
</tr>
</tbody>
</table>

![Background: Melanoma Prognosis Table]

Definitions

- Partial Response (PR): A decrease in the size of a tumor in response to treatment
- Complete Response (CR): The disappearance of all signs of cancer in response to treatment
- Stable Disease (SD): Cancer that is neither progressing or responding
- Objective Response Rate (ORR): PR + CR
- Progression Free Survival (PFS): Time from randomization to disease progression
- Overall Survival (OS): Time from randomization to death

![Definitions Diagram]

Treatment: Historical

- Surgery is the primary treatment for resectable melanoma, stage I – III.
- Often curative, especially in early stage disease
- Patients with metastatic disease have historically received two treatments:
  - Dacarbazine-based chemotherapy
    - 7 - 20% ORR, PFS 1.5 - 2 months
  - Interleukin-2
    - 16% ORR, 6% CR

![Treatment: Historical Diagram]

Treatment: New Agents

- Tyrosine Kinase Inhibitors
  - BRAF
    - Vemurafenib (Zelboraf®, 2011)
    - Dabrafenib (Tafinlar®, 2013)
  - MEK
    - Trametinib (Mekinist®TM, 2014)
- Immune Checkpoint Inhibitors
  - Ipilimumab (Yervoy®, 2011)*
  - Pembrolizumab (Keytruda®, 2014)
  - Nivolumab (Opdivo®, 2014)

![Treatment: New Agents Diagram]
**BRAF Inhibitors: Mechanism**

- Inhibits the activity of a mutant form of the serine-threonine protein kinase, BRAF.
- About 90% of pts with melanoma will have the BRAF V600E mutation.

**BRAF Inhibitors: Vemurafenib Efficacy**

- **Patients:**
  - Unresectable stage IIIC or stage IV melanoma with the BRAF V600E mutation
  - No prior treatment for their disease
  - Age > 18 y.o.
  - Life expectancy of > 3 months
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
  - Adequate hematologic, hepatic, and renal function

- **Multicenter, Phase III, randomized open-label trial comparing vemurafenib 960mg PO twice daily to dacarbazine 1000mg/m² IV q 3 weeks**
  - **Primary endpoints:** OS and PFS
  - **Secondary endpoints:**
    - Response rate
    - Duration of response
    - Time to response

**BRAF Inhibitors: Dabrafenib Efficacy**

- Multicenter, Phase III, randomized, open-label trial comparing dabrafenib 150mg PO twice daily to dacarbazine 1000mg/m² IV q 3 weeks
- Primary endpoints: PFS as assessed by investigator
- Secondary endpoints:
  - PFS as assessed by independent review committee
  - OS
  - ORR
  - PFS after crossover
  - Duration of response
  - Quality of Life
  - Safety
  - Tolerability


- Patients:
  - Unresectable stage IIIIC or stage IV melanoma with the BRAF V600E mutation
  - No prior treatment for their disease, except interleulin-2
  - Age > 18 y.o.
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
  - Adequate hematologic, hepatic, and renal function


- 483 pts screened
- 250 pts randomized
- 187 pts dabrafenib treated
- 63 pts dacarbazine treated
- 4 not treated


- 30/187 pts (11%) died in the dabrafenib arm vs. 9/63 pts (14%) in the dacarbazine arm
- Overall survival HR: 0.61 (95% CI: 0.25 – 1.48)
  - Not statistically significant
  - Potentially confounded by crossover from dacarbazine to dabrafenib at time of disease progression


**BRAF Inhibitors: Dabrafenib Efficacy**

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**BRAF Inhibitors: Dabrafenib Efficacy**

**BRAF Inhibitors: Dabrafenib Efficacy**

**BRAF Inhibitors: Dabrafenib Efficacy**

**BRAF Inhibitors: Adverse Effects**

- Frequent:
  - Hyperkeratosis: 12.5% vs. 6.3%
  - Squamous Cell Carcinoma/Keratoacanthoma: 6.4% vs. 19.9%
  - Rash: N/R vs. 5.1%
  - Nausea: 8.6% vs. 8.6%
  - Vomiting: 5.9% vs. 5.9%
  - Diarrhea: 31.1% vs. 19.9%
  - Anorexia: 21.1% vs. 5.1%
  - Fatigue: 13.1% vs. 7.9%
  - Headache: 18.2% vs. 8.6%
  - Pyrexia: 7.9% vs. 5.1%
  - Neutropenia: <1% vs. <1%


**BRAF Inhibitors: Adverse Effects**

- **Serious:**
  - Retinal Vein Occlusion: 12.3% vs <10%
  - Prolonged QT: 2-13% vs N/R

- 38% of patients taking vemurafenib required one or more dose reduction(s) due to adverse events (AEs)
- 28% of pts taking dabrafenib required one or more dose reduction(s) due to adverse events
- 3% of pts discontinued drug due to AEs

**Vemurafenib**
- FDA approved for 1st line treatment of unresectable stage IIIC or stage IV melanoma in patients with a BRAF V600E mutation
- Dose = 960mg PO twice daily
  - Can be taken with or without food
- Median PFS: 5.3 months vs 1.6 months with dacarbazine (an improvement of 3.7 months)
- OS at 6 months: 84% vs 64% with dacarbazine

**Dabrafenib**
- FDA approved for 1st line treatment of unresectable stage IIIC or stage IV melanoma in patients with a BRAF V600E mutation
- Dose = 150mg PO twice daily
  - Should be taken 1 hour before or 2 hours after a meal
- Median PFS: 5.1 months vs 2. months with dacarbazine (an improvement of 2.4 months)
- Dabrafenib can also be combined with a MEK inhibitor... stay tuned

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**MEK Inhibitors: Trametinib Efficacy**

- Multicenter, Phase III, randomized, open label trial comparing trametinib 2mg PO once daily to dacarbazine 1000mg/m² or paclitaxel 175mg/m² IV q 3 weeks
- **Primary endpoint:** PFS
- **Secondary endpoints:**
  - OS
  - ORR
  - Duration of response
  - Safety


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**MEK Inhibitors: Mechanism**

- Inhibits the activity of the protein tyrosine kinase, Mitogen-activated Extracellular signal regulated Kinase (MEK) 1 & 2
- Can be combined with a BRAF inhibitor to increase efficacy of both agents

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**MEK Inhibitors: Trametinib Efficacy**

- **Patients:**
  - Unresectable stage IIIC or stage IV melanoma with the BRAF V600E or V600K mutation
  - Pts could have received 1 prior treatment for their disease, as long as that treatment wasn’t:
    - BRAF inhibitor
    - MEK inhibitor
    - Ipilimumab
  - Age > 18 y.o.
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
  - Adequate organ function

MEK Inhibitors: Trametinib Efficacy


- 1022 pts screened
- 322 pts randomized
- 214 pts trametinib
- 211 pts treated
- 3 pts not treated

- 108 pts chemotherapy
- 99 pts treated
- 9 pts not treated

- 700 pts excluded


MEK Inhibitors: Trametinib Efficacy

![Graph showing progression-free survival](image)

- Hazard ratio: 0.54 (95% CI: 0.31-0.90, P=0.02)
- Months since Randomization: 0 1 2 3 4 5 6 7 8


MEK Inhibitors: Trametinib Efficacy

- Frequent:
  - Rash (57%)
  - Diarrhea (43%)
  - Fatigue (26%)
  - Peripheral edema (26%)
  - Acneiform dermatitis (19%)
  - Nausea/Vomiting (18%/13%)
  - Alopecia (17%)
  - Hypertension (15%)
  - Constipation (14%)

- Serious:
  - Ocular events (9%)
  - Blurred vision
  - Choriretnopathy
  - Ejection fraction (7%)
  - Cardiac events (<1%)

- 35% of pts required dose interruptions
- 27% of pts required dose reductions

MEK Inhibitors: Summary

- Trametinib monotherapy
  - FDA approved for 1st line treatment of unresectable stage IIIC or stage IV melanoma in patients with a BRAF V600E or V600K mutation
  - Dose = 2mg PO once daily
  - Should be taken 1 hour before or 2 hours after a meal
  - Median PFS: 4.8 months with trametinib vs 1.5 months with chemotherapy (an improvement of 3.3 months)
  - OS at 6 months: 86% with trametinib vs 67% with chemotherapy
  - Combination therapy...

MEK Inhibitors: Trametinib AEs

- Frequent:
  - Rash (57%)
  - Diarrhea (43%)
  - Fatigue (26%)
  - Peripheral edema (26%)
  - Acneiform dermatitis (19%)
  - Nausea/Vomiting (18%/13%)
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- 27% of pts required dose reductions

Dabrafenib + Trametinib

- Blocks the RAS pathway at 2 different points
- Provides some interesting benefits

Receptor Signal

Cell Proliferation

ERK

Nuclear signaling

RAS

RAF

MEK
Dabrafenib + Trametinib: Efficacy

- Multicenter, Phase III, randomized, open label trial comparing dabrafenib 150mg PO twice daily + trametinib 2mg PO once daily to vemurafenib 960mg PO twice daily
- Primary endpoint: OS
- Secondary endpoints:
  - PFS
  - ORR
  - Duration of response
  - Safety


Dabrafenib + Trametinib: Efficacy

Patients
- Unresectable stage IIIIC or stage IV melanoma with the BRAF V600E or V600K mutation
- No prior treatment for their melanoma
- Age > 18 y.o.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
  - Especially cardiac function


Dabrafenib + Trametinib: Efficacy

1645 pts screened
704 pts randomized
352 pts dabrafenib + trametinib treated
2 not treated
352 pts vemurafenib treated
3 not treated
941 pts excluded


Dabrafenib + Trametinib: AEs

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib + Trametinib</th>
<th>Vemurafenib</th>
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</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>53%</td>
<td>21%</td>
</tr>
<tr>
<td>Nausea</td>
<td>35%</td>
<td>38%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32%</td>
<td>38%</td>
</tr>
<tr>
<td>Chills</td>
<td>31%</td>
<td>8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29%</td>
<td>15%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>24%</td>
<td>51%</td>
</tr>
<tr>
<td>Rash</td>
<td>22%</td>
<td>43%</td>
</tr>
<tr>
<td>Hand-food syndrome</td>
<td>4%</td>
<td>25%</td>
</tr>
<tr>
<td>Hyperkeratosis/Skin papilloma</td>
<td>6%</td>
<td>45%</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>1%</td>
<td>18%</td>
</tr>
<tr>
<td>↓ Ejection Fraction</td>
<td>8%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Dabrafenib + Trametinib: Summary
- FDA approved for 1st line treatment of unresectable stage IIIC or stage IV melanoma in patients with a BRAF V600E or V600K mutation
- Dose = Dabrafenib 150mg PO twice daily + Trametinib 2mg PO once daily
- Both medications should be taken 1 hour before or 2 hours after a meal
- Median PFS: 11.4 months with the combination vs 7.3 months with vemurafenib (an improvement of 4.1 months)
- Median OS: Not reached in the combo group vs 17.2 months in the vemurafenib group

Anti-PD-1: Mechanism
- Programmed cell Death protein 1 (PD-1) is a receptor that is expressed on activated T-cells and pro-B-cells that is used to down-regulate the immune system
  - When the PD-1 receptor on a T-cell is stimulated by one of its ligands (PD-L1 & PD-L2), T-cell activation is prevented
  - This promotes immune tolerance
  - Useful in preventing autoimmunity
  - Many tumors express PD-L1 & PD-L2 on their cell surfaces, essentially turning off T-cells that might recognize & destroy the tumor

Anti-PD-1: Nivolumab Efficacy
- Phase III, randomized, open label trial comparing nivolumab 3mg/kg IV q2w to dacarbazine 1000mg/m² IV q3w or paclitaxel 175mg/m² + carboplatin AUC 6 IV q3w
  - Primary endpoints: ORR, OS
  - Secondary endpoints:
    - PFS
    - Tumor PD-L1 expression as a predictive marker for ORR/OS
  - 268 pts received nivolumab; 102 pts received chemotherapy

Anti-PD-1: Pembrolizumab Efficacy
- Expansion cohort of a phase I, randomized, dose-comparison trial comparing pembrolizumab 2mg/kg IV q3w to pembrolizumab 10mg/kg IV q3w
  - Primary endpoint: ORR
  - Secondary endpoints:
    - Duration of response
    - PFS
    - OS

Patients
- Advanced melanoma who’s disease progressed after anti-CTLA-4 (ipilimumab) therapy, and if BRAF V600 mutation positive, a BRAF inhibitor

Results
- ORR: 32% with nivolumab vs 17% with chemotherapy
- OS: Not reported yet
- Median duration of response: Not reached in nivolumab group vs 3.6 months in the chemotherapy group

Volume 372, Issue 1, Pages 30-39.

An: - PD-1:

**Pembrolizumab Efficacy**

- Patients:
  - Advanced melanoma who's disease progressed after anti-CTLA-4 (ipilimumab) therapy, and if BRAF V600 mutation positive, a BRAF inhibitor
  - Age > 18 y.o.

- Results:
  - ORR: 26% in the 2mg/kg arm vs 26% in the 10mg/kg arm


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**Adverse Effects**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Nivolumab*</th>
<th>Pembrolizumab*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>30%</td>
<td>47%</td>
</tr>
<tr>
<td>Nausea</td>
<td>N/R</td>
<td>30%</td>
</tr>
<tr>
<td>Pruritus*</td>
<td>19%</td>
<td>30%</td>
</tr>
<tr>
<td>Cough</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Rash</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>N/R</td>
<td>20%</td>
</tr>
<tr>
<td>Constipation</td>
<td>N/R</td>
<td>20%</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>N/R</td>
<td>20%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11%</td>
<td>17%</td>
</tr>
<tr>
<td>Increased LFTs*</td>
<td>Up to 28%</td>
<td></td>
</tr>
</tbody>
</table>


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**Adverse Events**

- Serious
  - Nivolumab:
    - Immune-mediated pneumonitis (3.4%) - Can be fatal
    - Immune-mediated colitis (2.6%) - Requires close monitoring and management with steroids or other immunosuppressants
    - Immune-mediated hepatitis (2.8%, 1.1% require steroids) - Immune-mediated nephritis/renal dysfunction (3%, 0.7% require steroids)
    - Immune-mediated endocrine disorders
      - Hypothyroidism (8%); Hyperthyroidism (3%)
      - Adrenal insufficiency, pancreatitis (1% each)

Anti-PD-1: Adverse Events

- Serious
  - Pembrolizumab:
    - Immune-mediated pneumonitis (2.9%)
      - Can be fatal
    - Immune-mediated colitis (1%)
      - Requires close monitoring and management with steroids or other immunosuppressants
    - Immune-mediated hepatitis (0.5%)
    - Immune-mediated nephritic/renal dysfunction (0.7%)
    - Immune-mediated endocrine disorders
      - Hypothyroidism (1.5%)
      - Hyperthyroidism (8.3%)
      - Hypophysitis (0.5%)
    - Pancreatitis (<1%)


Anti-PD-1 Inhibitors: Summary

- Nivolumab
  - FDA approved for treatment of unresectable or metastatic melanoma in patients who have progressed through ipilimumab and if BRAF V600 mutation positive, a BRAF inhibitor
    - Received accelerated approval – trials still ongoing
    - Dose = 3mg/kg IV q 2 weeks
    - Must monitor for immune-mediated toxicities!
      - If present, initiate prednisone 1-2mg/kg/day
    - 32% ORR

- Pembrolizumab
  - FDA approved for treatment of unresectable or metastatic melanoma in patients who have progressed through ipilimumab and if BRAF V600 mutation positive, a BRAF inhibitor
    - Received accelerated approval – trials still ongoing
    - Dose = 2mg/kg IV q 3 weeks
    - Must monitor for immune-mediated toxicities!
      - If present, initiate prednisone 1-2mg/kg/day
    - 26% ORR

Conclusions

- Many new and exciting treatment options for patients with advanced melanoma have recently become available
  - New treatment options offer better response rates than previous standards of care
  - Newer treatment options offer better PFS & OS than traditional chemotherapy
- Many new questions have arisen:
  - Tyrosine kinase inhibitors:
    - Is it better to start with BRAF inhibitor and add a MEK inhibitor at time of progression or start patients on the combination at time of initial presentation?
  - Immune Checkpoint Inhibitors
    - Do complete responders maintain their response indefinitely, as is seen with interleukin-2?

Questions?

Obtaining CME/CE Credit

- If you would like to obtain continuing education credit for this activity, please visit:
  - http://nih.cds.pesge.com