Melanoma- Fighting the “Dark Side”

- Anna C. Pavlick, BSN, MSc, DO, MBA
- Professor of Medicine and Dermatology
- Director, NYU Melanoma Program
- Director, NYU Clinical Trials Office NYU Perlmutter Cancer Center
Disclosures

American Osteopathic College of Dermatology
Anna C. Pavlick, BSN, MSc, DO, MBA

• I have the following financial relationships to disclose:
  Consultant for: BMS, Merck, Novartis
  Research Support (funds go to NYU); BMS, Merck, Novartis, Celldex, Millineum, Genentech, Roche

• I will investigational in clinical trials in my presentation. I will not discuss off label use.
Overview

• Overview of Cutaneous Metastatic Melanoma

• Targeted Therapies
  BRAF inhibitors
  MEK inhibitors

• Checkpoint Inhibitors
  CTLA4 inhibition
  PD1 inhibition
  Combination therapy

• Conjugated Monoclonal Antibodies
Melanoma

- Most deadly of all skin cancers
- If caught early, it is 95% curable
- One person dies from melanoma every hour
- Only cancer in the US that is rising
- 1 in 50 Americans will be diagnosed with melanoma
- Once you have one melanoma you are 10 times more likely to develop another melanoma
- Risk for melanoma doubles if you have had more than 5 sunburns
- One or more blistering sunburn as a child doubles melanoma risk
- Use of tanning beds dramatically increases melanoma risk
Metastatic Disease

• Less than 5% of all patients survived for 5 years with metastatic disease prior to 2011
• With new therapies, approximately 25% of patients will survive metastatic disease.
• Disease response to therapy is approximately 75%
• 50% with metastatic disease develop brain metastases.
• 2 FDA approved therapies prior to 2011: Dacarbazine and Il-2-both with response rates between 6 and 15% and NO impact on overall survival.
• 2011-ipilimumab and BRAF inhibitors FDA approved and changed overall survival.
Unprecedented Progress: Two Different Approaches

Targeting MAP Kinase Pathway

Immune Checkpoint Inhibitors
Targeted Therapies
Mutations in Melanoma

- BRAF
- NRAS
- MEK
- KIT
- GNAQ
- GNA11
BRAF

• Mutated in approximately 50% of melanoma
• Most common mutation is V600E
• Other mutations- V600 K (20%), V 600D, 601
  – Sensitivity to BRAF inhibitors to be defined
• Younger age, fewer markers of chronic sun damage, trunk primary, superficial spreading melanoma or nodular subtype.
• Perhaps worse overall survival
MAPK and PI3K Pathways

- **KIT mut**
  - RTK
  - 20%
  - ~10-20% mucosal
  - ~10-20% acral

- **NRAS mut**
  - ~20-25%
  - ~10% cutaneous
  - ~9% mucosal
  - ~9% acral

- **BRAF mut**
  - ~50%
  - Primarily cutaneous melanomas

- **PI3K**
  - mTOR
  - Akt

- **Cell Responses**
The Target: B-RAF Kinase

- RAS
- BRAF$^{V600E}$
- MEK
- ERK

**MEKi**
- Trametinib

**BRAFi**
- Vemurafenib
- Dabrafenib

**ATP**

**RTK**

**Cellular Proliferation**
2nd Generation V600-Selective BRAF Inhibitors

Vemurafenib

Day 1

Day 15

Dabrafanib/GSK2118436

Pre

Week 10

### Disease Stage
- Unresectable stage IIIc
- M1a
- M1b
- M1c

### Percent Change from Baseline in Diameters of Target Lesions

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>Median PFS (Mos)</th>
<th>OS at 6 Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>48.6%</td>
<td>5.3</td>
<td>84%</td>
</tr>
<tr>
<td>DTIC</td>
<td>5.5%</td>
<td>1.6</td>
<td>64%</td>
</tr>
</tbody>
</table>
Possible Adverse Effects of BRAFi

- Arthralgias
- Myalgias
- Rash
- Hepatotoxicity
- Hand/Foot Syndrome
- Pyrexia
- Photosensitivity
- New cutaneous skin cancers (SCC, Melanoma)
Skin Toxicities-BRAFi

- Plantar-palmar Hyperkeratoses
- Verrucal Lesion
- Squamous Cell
Diffuse Macular Rash
From BRAF Inhibitor
Photosensitivity Secondary to BRAF Inhibitors
BRAF/MEK Inhibition
Progression Free Survival


Mono = Dabrafenib monotherapy
150/1 = Dabrafenib (150 mg) plus trametinib (1 mg)
150/2 = Dabrafenib (150 mg) plus trametinib (2 mg)
Figure 2. Overall Survival.
Shown are Kaplan–Meier estimates of overall survival in the intention-to-treat population (Panel A) and in patients with an elevated lactate dehydrogenase level at baseline (Panel B). The vertical lines indicate censoring of data.
MEK, BRAF & BRAF/MEK combination (1st line)

- Maximum percent reduction from baseline measurement
- Best confirmed response
  - Complete response
  - Partial response
  - Progressive disease
  - Stable disease

Disease stage
- M1c
- M1b
- M1a
- IIIC
- Unknown

Dabrafenib 150 mg BID
Dabrafenib 150 mg BID/Trametinib 2 mg QD

Flaherty KT et al. NEJM 2012
Rash on MEK Inhibitor
Erythematous Acneiform Rash Typical of MEK Inhibitors
Erythema Surrounding All Tattoos
Checkpoint Inhibitors
Anti-CTLA4 Monoclonal Antibodies for Melanoma

• Stimulate T cells to recognize cancer antigens and develop mechanisms for cell death—“taking the brakes off the immune system”

• Break tolerance of T cells to self antigens in order to permit anti-tumor response

• Potential side effects are autoimmune diseases
Ipilimumab Augments T-Cell Activation and Proliferation

T-cell activation

T-cell inhibition

T-cell remains active

Adapted from O’Day et al. Plenary session presentation, abstract #4, ASCO 2010.
Antigen recognition by T cells

T cell antigen receptor (TCR)

MHC

Antigen presenting cell

Processing

Antigen

Cytokines

Activation
Pivotal Phase 3 Study of Ipilimumab

- Due to the inclusion of the gp100 peptide vaccine comparator, the study was restricted to patients with HLA-A2*0201 genotype.
- All patients had been previously treated with one or more of the following: aldesleukin (IL-2), dacarbazine, temozolomide, fotemustine, or carboplatin.

- Primary Endpoint: Overall survival in ipilimumab + gp100 arm vs gp100 arm
**Ipilimumab Overall Survival**

1 Year OS = 46%
2 Year OS = 24%

**Table: Survival Rates**

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Ipilimumab + gp100 N=403</th>
<th>Ipilimumab + placebo N=137</th>
<th>gp100 + placebo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>2 year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Hodi et al NEJM 2010
Ipilimumab Toxicities

Management:
1) Early Detection
2) Early Consult
3) Early Treatment (Steroids)

- Thyroiditis (1.5-2.5%)
- Dermatitis (43.5%)
- Panhypopituitary Hypophysitis (4%)
- Adrenal failure (1.5-3%)
- ALT/AST rise (~30%*)
- Hepatitis (4%)
- Colitis Diarrhea (~30%)
Immune-Mediated Side Effects: Time to Onset

- Time-to-onset data are not available for hepatitis, neuropathy, and other immune-mediated side effects.
Nonconventional Kinetics Are Most Apparent With Pseudo-Progression

Pseudo-progression may occur when T-cell infiltration causes tumors to flare or new lesions to appear upon imaging\(^1\)

<table>
<thead>
<tr>
<th>Considerations when evaluating true progression vs pseudo-progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>May indicate progression</strong></td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
</tr>
<tr>
<td><strong>Symptoms of tumor enlargement</strong></td>
</tr>
<tr>
<td><strong>Tumor burden</strong></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>New lesions</strong></td>
</tr>
<tr>
<td><strong>Biopsy may reveal</strong></td>
</tr>
</tbody>
</table>

Ipilimumab: Response After Tumor Volume Increase

Screening

Week 12
Initial increase in total tumor burden (mWHO PD)

Week 16
Responding

Week 72
Durable & ongoing response without signs of IRAEs

Courtesy of K. Harmankaya and S. Hodi
Tumorous nodule with melanin pigment (macrophages and lymphocytes; no melanocytes)

Macrophages and lymphocytes are present, but no tumor cells
Skin Toxicity

A

B

Hair Depigmentation
Anti-PD1 Antibodies for Melanoma

• Immunotherapy for melanoma only available through clinical trials targets anti-programmed cell death 1 receptor.
• Targets PDL-1 and 2 receptors on tumor cells.
• As a single agent approximately 30% of patients with metastatic melanoma respond.
• Less of a chance of side effects when compared to ipilimumab. Side effects include rash, itching, diarrhea and pneumonitis.
• Given by vein every 2-3 weeks depending on PD1 compound.
• May be even better if combined with ipilimumab, but toxicity is also increased.
Role of PD-1 Pathway in Tumor Immunity

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells

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Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells

Role of PD-1 Pathway in Tumor Immunity

Sznol et al., ASCO, 2013
Best Responses in All Evaluable Patients in Sequenced Cohorts

- Patients who had radiographic progression with prior ipilimumab treatment.
- Patients who had stable disease with prior ipilimumab treatment.
Pembrolizumab (anti-PD1) Skin Rash
Dual Checkpoint Blockade
Blocking CTLA-4 and PD-1

**CTLA-4 Blockade (ipilimumab)**
- Dendritic cell
  - B7
  - CD28
  - CTLA-4
  - anti-CTLA-4
- T cell
  - MHC
  - TCR
  - +++
- Activation (cytokines, lysis, proliferation, migration to tumor)

**PD-1 Blockade (nivolumab)**
- T cell
  - MHC
  - TCR
  - PD-1
  - PD-L1
  - anti-PD-1
- Tumor cell
  - PD-1
  - PD-L2
  - anti-PD-1

Tumor Microenvironment
Eligible patients with unresectable stage III or IV melanoma
• Treatment-naïve
• BRAF WT (N = 100) or MT (N = 50)
• Stratified by BRAF status

Treatment -

BRAF WT (N = 100) or MT (N = 50)

Stratified by BRAF status

Double-blind

Treat until:
disease progression\(^a\) or unacceptable toxicity

Primary endpoint:
• ORR in BRAF WT patients
Secondary endpoints:
• PFS in BRAF WT patients
• ORR and PFS in BRAF MT patients
• Safety

\(^a\)Treatment beyond initial investigator-assessed RECIST v1.1- defined progression is permitted in patients experiencing clinical benefit and tolerating study therapy. Arm B patients have option to receive nivolumab monotherapy after progression. Upon confirmed progression and change of treatment, all patients are unblinded.

MT = mutation; PFS = progression-free survival; Q3W = every 3 weeks; WT = wild type
# Objective Response, Investigator-Assessed

<table>
<thead>
<tr>
<th></th>
<th>All Randomized Patients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIVO + IPI (N = 95)</td>
<td>IPI (N = 47)</td>
<td></td>
</tr>
<tr>
<td>ORR, % (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>59 (48, 69)</td>
<td>11 (4, 23)</td>
<td></td>
</tr>
<tr>
<td>P value for comparison</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best overall response, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>37</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>13</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Unable to determine</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>(Complete response + partial response)/(all randomized patients); 95% CI based on Clopper and Pearson method

<sup>b</sup>RECIST v1.1

CI = confidence interval
PD-1 Inhibition after Ipilimumab Progression

7/1/13

3/20/14
PFS in All Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=95)</th>
<th>IPI (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or disease progression, n/N</td>
<td>42/95</td>
<td>32/47</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR</td>
<td>3.0 (2.8-5.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.39 (0.25, 0.63)</td>
<td>--</td>
</tr>
</tbody>
</table>
PFS in Patient Subgroups: M1c Stage

<table>
<thead>
<tr>
<th>M1c stage subgroup</th>
<th>Death or disease progression, n/N</th>
<th>Median PFS, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>22/44</td>
<td>10.2 (4.1, NA)</td>
</tr>
<tr>
<td>IPI monotherapy</td>
<td>14/21</td>
<td>3.9 (2.7, 6.8)</td>
</tr>
</tbody>
</table>

Number of Patients at Risk
Nivolumab + Ipilimumab: 44, 33, 27, 22, 10, 0
Ipilimumab: 21, 11, 6, 5, 1, 0

Progression-Free Survival per Investigator (months)
PFS in Patient Subgroups:
BRAF V600 Mutation-positive

<table>
<thead>
<tr>
<th>BRF V600 mutant subgroup</th>
<th>Death or disease progression, n/N</th>
<th>Median PFS, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>12/23</td>
<td>8.5 (2.8–NR)</td>
</tr>
<tr>
<td>IPI monotherapy</td>
<td>7/10</td>
<td>2.7 (1.0–5.4)</td>
</tr>
</tbody>
</table>

Patients Alive and Progression-Free (%)

- Nivolumab + Ipilimumab (N = 23)
- Ipilimumab (N = 10)
## Safety Summary

<table>
<thead>
<tr>
<th>Patients Reporting Event, %</th>
<th>NIVO + IPI (N = 94)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IPI (N = 46)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>91</td>
<td>54</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>46</td>
<td>28</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>46</td>
<td>26</td>
</tr>
<tr>
<td>M1c disease</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>Treatment-related death</td>
<td></td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Safety was evaluated in all patients who received at least one dose of study treatment

<sup>b</sup>Associated with ventricular arrhythmia, pneumonitis, and pneumonia/hypercalcemia

AEs = adverse events
## Most Common Treatment-Related Select AEs

<table>
<thead>
<tr>
<th>Patients Reporting, %</th>
<th>NIVO + IPI (N = 94)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IPI (N =46)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td><strong>Gastrointestinal AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>11</td>
</tr>
<tr>
<td>Colitis</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td><strong>Hepatic AEs</strong></td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>ALT increased</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>AST increased</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td><strong>Pulmonary AEs</strong></td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td><strong>Renal AEs</strong></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Endocrine AEs</strong></td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td><strong>Skin AEs</strong></td>
<td>71</td>
<td>10</td>
</tr>
<tr>
<td>Rash</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35</td>
<td>1</td>
</tr>
</tbody>
</table>

- Apart from endocrinopathies, the majority (~80%) of treatment-related select AEs resolved when immune-modulating medications were utilized.
Most grade 3/4 treatment-related select AEs occurred during the combination phase.
Conjugated Monoclonal Antibody
Glembatumumab
CR011-vcMMAE-Glembatumumab

- Fully human monoclonal IgG\(_2\) antibody (CR011) conjugated to cytotoxic monomethyl auristatin-E (MMAE)
  - MMAE is related to dolastatin, a marine-peptide derived tubulin inhibitor
- Enzyme-cleavable valine-citrulline linker
  - Stable in the circulation
- Antibody targets glycoprotein NMB (GPNMB)
  - Originally identified by high throughput genomic screening technologies
  - Overexpressed in melanoma and other cancers
CR011-vcMMAE: Mechanism of Action

1. CR011-vcMMAE binds to GPNMB on the surface of cancer cells
2. After internalization, the valine-citrulline linker is cleaved by endosomal enzymes
3. Free MMAE inhibits tubulin polymerization, leading to cell death
Specific expression of GPNMB in patient tumor biopsies

Presented at ASCO 2008
CR011-vcMMAE: Phase I/II Study in Patients with Melanoma

– Patient Population:
  • Unresectable Stage III or Stage IV melanoma
  • Progressive disease at study entry
  • Any prior cytokines or immunotherapy
  • ≤ 1 prior cytotoxic regimen
  • Stable brain metastases allowed

– Study Design:
  • Phase I enrolls sequential cohorts of patients at increasing doses
  • IV infusion once every 3 weeks (IV Q3W)
  • Starting dose 0.03 mg/kg IV Q3W
  • Phase II Simon 2-stage design
  • Primary endpoint is response rate, n=32
Skin Rash from Glembatumumab
Conclusions:

• Metastatic melanoma is no longer an incurable, universally fatal disease.
• Immunotherapy has provided patients with long term, durable responses.
• Targeted therapy has provided a rapid mechanism for disease control in BRAF mutated patients.
• We have made dramatic strides in the treatment and long term control of melanoma, however, more work needs to be done to cure everyone.
• Participation in a clinical research trial remains the gold standard for patients with metastatic melanoma.
Acknowledgements:

• Thank you to all the patients who participated in our melanoma research trials and changed the outcome of this disease.
• Thank you to all the patient who agreed to having photos taken of their responses or toxicity, so that we could learn from them.
• Thank you to all of my referring physicians who trust their patients to my care.
• Finally, thank you to my dedicated staff for their dedication to our patients and most importantly for putting up with me.