Emerging Trends & Strategies in the Treatment & Management of Metastatic Melanoma

Evan J. Lipson, MD
Johns Hopkins University School of Medicine
Sidney Kimmel Comprehensive Cancer Center
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Objectives

• Analyze clinical data evaluating the safety and efficacy of targeted therapies and immunotherapies in the treatment of metastatic melanoma
• Review the integration of BRAF testing in patients who have been diagnosed with metastatic melanoma
• Identify patients with metastatic melanoma who are candidates for targeted therapies and immunotherapeutic regimens
• Discuss recently updated NCCN and ASCO management guidelines on the treatment of metastatic melanoma
• Describe the adverse events associated with BRAF inhibitors (and immunotherapies) and discuss strategies for anticipating and managing these events
I have no disclosures.

I will be discussing the following unapproved drugs:
Nivolumab, Lambrolizumab (anti-PD-1)
BMS-936559, MPDL3280A (anti-PD-L1)

Lifetime Risk of Developing Cutaneous Melanoma in the US

American Cancer Society: an estimated 9,480 people in the U.S. died from advanced melanoma in 2013.

Available & Emerging Therapies

- **Chemotherapy**
  - dacarbazine, temozolomide, platinum, etc.
  - Limited role

- **Targeted therapy** (Oncogenic pathway inhib.)
  - Selective BRAF and MEK Inhibitors
  - Tyrosine Kinase Inhibitors (cKIT)

- **Immunotherapy**
  - Interleukin-2
  - T cell therapy
  - Ipilimumab (Yervoy)
  - Nivolumab, Pembrolizumab (formerly lambrolizumab) (anti-PD-1)
  - MPDL3280A, BMS-936559 (anti-PD-L1)
February 21, 2010: BRAF inhibitor (vemurafenib)

Oncogenic Pathway Inhibition

Testing:
Stage IIB and above
Include CKIT, NRAS, PIK3CA
Pathway Therapy

• Vemurafenib (Zelboraf) was FDA approved in August 2011 for metastatic melanoma harboring a BRAF V600E mutation
• The name "vemurafenib" comes from V600E mutated BRAF.

Efficacy & Safety: Vemurafenib

• BRIM-3 trial: phase 3 randomized clinical trial comparing vemurafenib with dacarbazine in 675 patients with untreated, metastatic V600E mutant melanoma

• Overall response rate:
  – 48.4% vemurafenib
  – 5.5% dacarbazine

Chapman et al, NEJM, 2011
Efficacy & Safety: Vemurafenib

• Side effects:
  – Arthralgia, rash, fatigue, alopecia
  – Keratoacanthoma or squamous cell carcinoma
  – Photosensitivity
  – Nausea, diarrhea
  – BRIM-3 trial: 38% of patients required dose modification because of side effects.

Dabrafenib (Tafinlar)

• BRAF inhibitor (GSK)
• FDA approved in 2013 for unresectable BRAF V600E/K melanoma
• Dabrafenib vs. dacarbazine:
  – Response rates: 50% vs 7% (Hauschild, Lancet, 2012)
  – Nine of 10 patients with melanoma brain metastases had reductions in size of brain lesions.
  – In 28 patients with BRAF-mutant non-melanoma solid tumors, anti-tumor activity was noted in GIST, papillary thyroid cancer, NSCLC, ovarian cancer and colorectal cancer. (Falchook, Lancet, 2012)
Efficacy & Safety: Dabrafenib

• Side effects:
  – Fever
  – Arthralgia, fatigue
  – Keratoacanthoma or squamous cell carcinoma
  – Headache

Trametinib (Mekinist)

• MEK inhibitor (GSK)
• FDA approved in 2013 for unresectable BRAF V600E/K melanoma
• Trametinib vs. dacarbazine:
  – Response rates: 22% vs 8% (Flaherty, *NEJM*, 2012)
  – Little to no clinical activity in patients who had previously progressed on BRAF inhibitors (Kim, *Journal of Clinical Oncology*, 2013)

Efficacy & Safety: Trametinib

• Side effects:
  – Rash (~80%)
  – Diarrhea (~40%)
  – Peripheral edema
  – Cardiomyopathy
  – Interstitial lung disease
  – Retinal vein occlusion & retinopathy

Dabrafenib and Trametinib

- January 2014: FDA approves combination of trametinib and dabrafenib for unresectable or metastatic V600E/K melanoma
- Approval based on demonstration of durable response rate. Improvements in disease-related symptoms and overall survival not yet shown for the combination.
Dabrafenib and Trametinib

- 162 patients randomized to D/T vs D
- Primary end points: incidence of cutaneous squamous-cell carcinoma, progression-free survival, response rate, duration of response and safety.
- Median follow-up: 14 months
  – (Flaherty, NEJM, 2012)

**Dabrafenib and Trametinib**

<table>
<thead>
<tr>
<th></th>
<th>Overall Response Rate (%)</th>
<th>Complete Response (%)</th>
<th>Median Duration of Response (mos)</th>
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<tbody>
<tr>
<td><strong>Investigator Assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D + T</td>
<td>76</td>
<td>9</td>
<td>10.5</td>
</tr>
<tr>
<td>D alone</td>
<td>54</td>
<td>4</td>
<td>5.6</td>
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<tr>
<td><strong>Independent Radiology Review Committee Assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D + T</td>
<td>57</td>
<td>9</td>
<td>7.6</td>
</tr>
<tr>
<td>D alone</td>
<td>46</td>
<td>7</td>
<td>7.6</td>
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</tbody>
</table>
Managing side effects of BRAFi / MEKi

- **Rash**: oral antibiotics (doxy), topical antibacterial agents (clindamycin 1% solution or triclosan wash)
- **Cardiomyopathy**: Assess LVEF at baseline, after one month of treatment, and every 2 to 3 months thereafter
- **Retinal Vein Occlusion (RVO) and Retinal Pigment Epithelial Detachment (RPED)**: Perform ophthalmologic evaluation for any visual disturbances
- **Interstitial Lung Disease (ILD)**: Pulmonary eval for new or progressive unexplained pulmonary symptoms (cough, dyspnea, hypoxia, infiltrates)

Managing side effects of BRAFi / MEKi

- **Skin Toxicity**: Regular dermatologic evaluations
- **WOCBP**: can cause fetal harm
- **Fevers**: infectious workup, steroids
- **Hyperglycemia**: monitor serum glucose levels
- **Glucose-6-Phosphate Dehydrogenase Deficiency**: monitor for hemolytic anemia
Targeted therapy

• What I tell my patients:
  – Therapy often works quickly and effectively; good for patients who need an immediate response
  – In general, responses are not durable: resistance often develops after 6-8 months

Available & Emerging Therapies

• Chemotherapy
  – dacarbazine, temozolomide, platinum, etc.
  – Limited role

• Targeted therapy (Oncogenic pathway inhib.)
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• Immunotherapy
  – Interleukin-2
  – Iplimimumab (Yervoy)
  – Nivolumab, Pembrolizumab (formerly lambrolizumab) (anti-PD-1)
  – MPDL3280A, BMS-936559 (anti-PD-L1)
Why Immunotherapy?

- Melanoma is perhaps the most immunogenic human cancer
- Human immune system can attack with virtually unlimited precision
- Unlike targeted therapy, can adapt to ongoing tumor mutations and avoid drug resistance
- Responses are often durable (immune memory)

Efficacy & Safety: Interleukin-2

- Administered in ICU; ~100 centers in U.S.
- Approximately 15-20% response rate
- 5% long-term responders (cure?)

- Side effects: Hypotension, tachycardia, capillary leak syndrome, altered mental status
Efficacy & Safety: Ipilimumab

- 2011: Ipilimumab (Yervoy, anti-CTLA-4) was FDA-approved for the treatment of metastatic melanoma after a 676-patient randomized study demonstrated improved overall survival.

Survival: Ipilimumab

Adapted from Hodi et al, NEJM 2010
Efficacy and Safety: Ipilimumab

- Serious (grade 3-4) drug-related adverse events occurred in 17-23% of patients, with a 2% mortality rate.
- Immune-related Adverse Events:
  - Colitis (diarrhea, abd pain, blood in stool)
  - Hepatitis (jaundice, LFT rise)
  - Dermatitis (pruritus, rash, rare TEN)
  - Hypophysitis (headache, endocrine dysfunction)
  - Nephritis (creatinine rise)
  - Neuropathies (numbness, weakness, paresthesias)
  - Others

Understanding irAEs: Immune Checkpoints

Adapted from Sharpe et al., Nat Rev 2002

Management of Immune-related Adverse Events (irAEs)

- irAEs are diagnosed by exclusion: rule out other etiologies (e.g. infection, neoplasm, metabolic causes, effects of other drugs)
- Management for most irAEs based on severity
- In general:
  - grade 1-2: supportive care; +/- withhold ipilimumab
  - grade 3-4: corticosteroids; discontinue ipilimumab
irAE Management Example: Colitis

- **Severe enterocolitis**
  - Permanently discontinue ipilimumab
  - Systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent); infliximab if refractory
  - Upon improvement to ≤ grade 1, taper steroids over ~4 weeks

- **Moderate enterocolitis**
  - Withhold ipilimumab, administer anti-diarrheal Rx
  - If moderate enterocolitis persists for > 1 week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent

Adapted from Sharpe et al., Nat Rev 2002

Emerging immunotherapies

Adapted from Sharpe et al., Nat Rev 2002
Nivolumab (anti-PD-1)

- A monoclonal antibody made by Bristol-Myers Squibb
- Activates T cells by blocking PD-1 on T cells, from binding to PD-L1 “partner molecule” on tumor cells
- Well-tolerated in patients with treatment-resistant cancers in a first-in-human study led by Johns Hopkins investigators; tumor regressions were seen in patients with melanoma, kidney, colon, and lung cancer (Brahmer et al., J Clin Oncol 2010).

First-in-human clinical trial of nivolumab (anti-PD-1) in patients with advanced cancers
(Brahmer et al., JCO 2010)

Eligible patients: treatment-refractory metastatic lung cancer, melanoma, kidney, colon, or prostate cancer
Durable response to nivolumab (anti-PD-1) off-therapy

71-year-old man with colorectal cancer
Disease progression through surgery and chemotherapy
Partial response after one dose of nivolumab
Received four more doses over 6 months → complete response
CR maintained >5 yrs off therapy

(Lipson et al., CCR 2013)

Paradigm #1

• Blockade of the PD-1 immune checkpoint pathway can induce durable antitumor responses which can persist even after discontinuation of therapy
  – Distinct from chemo, oncogenic pathway inhibitors (e.g., BRAF inhibitors)
  – Suggests a shift in equilibrium between tumor and host
  – Supports use of checkpoint blockade early in the course of therapy in appropriate patients
Immune-related Responses to nivolumab (anti-PD-1)

- 76 y.o. man w/ clear cell kidney cancer
- PD after HDAC inhibitor (mocetinostat), sunitinib, sorafenib
- Mixed response after 1 dose of nivolumab, then PR after two more doses
- Brain lesion: resected; no tumor seen
- CR without further therapy, ongoing at >5 years

(Lipson et al., CCR 2013)

Paradigm #2

- Response patterns to checkpoint blockade therapies, including anti-PD-1, are unique, necessitating technologies that can distinguish immune cell activity from tumor growth
  - Novel radiotracers?
  - Circulating tumor cells or DNA?
Successful re-induction with nivolumab (anti-PD-1)

• 55 y.o. woman w/ metastatic melanoma; mixed response after 1 dose of nivolumab
• PR after additional doses; maintained for 16 months off therapy
• Developed new thoracic adenopathy; biopsy confirmed melanoma
• Re-induction nivolumab → PR for 21 months → PD
• Received ipilimumab → SD

(Lipson et al., CCR 2013)

Paradigm #3

• Re-induction therapy with anti-PD-1 can reset the equilibrium between the tumor and the host's immune system, re-establishing immune-based control of tumor growth
  – Maintenance therapy to preserve equilibrium?
  – Early detection of recurrence?
Eligibility: Advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1–5 systemic therapies. Cohorts of MEL patients were expanded at 0.1, 0.3, 1, 3, and 10 mg/kg

* Nivolumab dose administered IV every 2 weeks

Rapid PD or clinical deterioration
Follow-up every 8 weeks x 6 (48 weeks)
Treat to confirmed CR, worsening PD, unacceptable toxicity, or 12 cycles (96 weeks)

Unacceptable toxicity

CR/PR/SD or PD but clinically stable

8-week treatment cycle

Tumor regressions in patients with melanoma receiving nivolumab therapy


Topalian SL et al. JCO 2014
Nivolumab

- Median overall survival: 16.8 months
- 1-year survival rate: 62%
- 2-year survival rate: 43%
- 12 of 17 (71%) of patients who discontinued therapy for reasons other than disease progression maintained responses off-therapy for at least 16 weeks (range, 16 to 56+ weeks)

Kaplan-Meier curve of overall survival in 107 nivolumab-treated patients with melanoma

Topalian et al. JCO 2014
Presented by: Antoni Ribas, ASCO 2013

Individual Patients Treated With Lambrolizumab

Percent Change From Baseline in Longest Diameter of Target Lesion

-100 -80 -60 -40 -20 0 20 40 60 80 100 120 140 160

IPI-Naive
IPI-Pretreated

Ipilimumab + Nivolumab: Best responses in all evaluable patients in concurrent cohorts

Next step: phase III trial...
### NCCN Guidelines Version 3.2014

**Melanoma**

#### Systemic Therapy Options for Advanced or Metastatic Melanoma

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Active Regimens</th>
</tr>
</thead>
</table>
| Ipilimumab (category 1)
| Trametinib (category 1) |
| Vemurafenib (category 1) |
| Dabrafenib (category 1) |
| Dabrafenib + trametinib |
| Clinical trial |
| High-dose IL-2 |
| Imatinib for C-KIT mutated tumors |
| Dacarbazine |
| Temozolomide |
| Albumin-bound paclitaxel |
| Dacarbazine- or temozolomide-based combination chemotherapy/biochemotherapy (including cisplatin and vinblastine with or without IL-2, interferon alfa) (category 2b) |
| Paclitaxel (category 2b) |
| Paclitaxel/carboplatin (category 2b) |

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**Science Breakthrough of the Year**

**Cancer Immunotherapy**

Science, Dec 2013
“As the anecdotes coalesce into data, there's another layer, too, a sense of paradigms shifting. Immunotherapy marks an entirely different way of treating cancer—by targeting the immune system, not the tumor itself. Oncologists, a grounded-in-reality bunch, say a corner has been turned and we won't be going back.”

– Jennifer Couzin-Frankel
Science, Dec 2013

ACKNOWLEDGEMENTS

Drs. Topalian, Sharfman, Pardoll, Taube, Brahmer, Drake
Johns Hopkins Cancer Immunology and Melanoma Programs
Talimogene laherparepvec (T-VEC)

- Oncolytic virus
- Durable response rate: 16% vs 2% GM-CSF
- Regression of non-injected tumors
- Phase III
  - primary end point (durable response rate) was met
  - secondary endpoint (overall survival) was not met, although there was a strong trend in favor of T-VEC (p=0.051).
Strategies for Combinatorial Therapy

- Target multiple coordinately-expressed immune checkpoints (e.g. PD-1, CTLA-4, LAG-3, KIR)
- Prime the tumor microenvironment to respond to checkpoint therapy
- Expand and activate cancer neo-antigen-specific T-cells into the tumor microenvironment
  - Immune agents (interferons, cytokines (e.g., IL-21), TCR-CD3 fusion proteins, Toll-Like receptor delivery)
  - Oncogenic pathway targeted agents (e.g., BRAF inhibitors)
  - Anti-VEGF therapies (e.g., bevacizumab)
  - Epigenetic modifiers (e.g., azacitadine)
  - Vaccines

PD-L1 Expression and Objective Response Rate

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>PDL1 + Positive</th>
<th>PDL1 - Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (Topalian, NEJM, 2012)</td>
<td>42</td>
<td>9/25 (36%)</td>
<td>0/17 (0%)</td>
</tr>
<tr>
<td>Nivolumab (Weber #9011)</td>
<td>44</td>
<td>8/12 (67%)</td>
<td>6/32 (19%)</td>
</tr>
<tr>
<td>MPDL3280A (Hamid #9010)</td>
<td>30</td>
<td>4/15 (27%)</td>
<td>3/15 (20%)</td>
</tr>
<tr>
<td>Nivolumab/ Ipilimumab (Callahan #3003)</td>
<td>27</td>
<td>4/10 (40%)</td>
<td>8/17 (47%)</td>
</tr>
<tr>
<td>Nivolumab (Grosso #3016)</td>
<td>34</td>
<td>7/16 (44%)</td>
<td>3/18 (17%)</td>
</tr>
</tbody>
</table>

Presented by: Walter J. Urba, MD, PhD
**Gene mutation frequency in melanoma and predicted sensitivities to targeted agents**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Frequency and Anatomic Site</th>
<th>Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>V600E/R/A/W/G/D</td>
<td>8% CSD, 58% non-CSD, 22% Acral/Mucosal (G266A)</td>
<td>Sensitive to: Vemurafenib (BRAF inhibitor)</td>
</tr>
<tr>
<td>NRAS</td>
<td>G12C/L/V/A/I/D G12M/V/R/P/D Q61H/ELV/PRR</td>
<td>10% Acral, 26% Mucosal, 19% CSD, 22% non-CSD (G166L)</td>
<td>Sensitive to: (pre-clinical) NRAS inhibition</td>
</tr>
<tr>
<td>KIT</td>
<td>WB579 V559A/D L770P K854E D816H</td>
<td>23% Acral, 10% Mucosal, 28% CSD (G201R)</td>
<td>Sensitive to: Imatinib (KIT inhibitor)</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>S33Y/P Y460H/Y</td>
<td>4% Overall (G2,53,34)</td>
<td>Preclinical progression of BRAF mutant melanoma (G2,53)</td>
</tr>
<tr>
<td>GNAQ</td>
<td>G209R/L/R</td>
<td>45% Uveal (G7)</td>
<td>Sensitive to: (pre-clinical) NRAS inhibition</td>
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</tbody>
</table>


http://www.plosone.org/article/info:doi/10.1371/journal.pone.0035309