Update on Therapy for Metastatic Melanoma

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AAD Annual Meeting
Washington, DC
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Emily Y. Chu, M.D., Ph.D.
F105: “Managing Melanoma”

DISCLOSURES
I do not have any relevant relationships with industry.
Metastatic melanoma

- Historically has a poor prognosis
  - Median survival around 6 – 9 months
  - 5-year survival <5%

Prior to 2011, no FDA-approved therapy shown to prolong survival
The pace of progress

- Ipilimumab approved in 2011
- Vemurafenib approved in 2011
- Dabrafenib approved in 2013
- Trametinib approved in 2013
- Pembrolizumab approved in 2014
- Nivolumab approved in 2015
- Talimogene laherparepvec approved in 2015
- Encorafenib and binimetinib approved in 2018
- Many promising agents in clinical trials
FDA approved medications for advanced melanoma

• Targeted kinase inhibitors
  – BRAF inhibitors (vemurafenib, dabrafenib, encorafenib)
  – MEK (trametinib, cobimetinib, binimetinib)

• Immunotherapy agents
  – Ipilimumab
  – PD-1 inhibitors (nivolumab, pembrolizumab)
  – Talimogene laherparepvec/T-VEC
FDA approved medications for advanced melanoma

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• Immunotherapy agents
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  – PD-1 inhibitors (nivolumab, pembrolizumab)
  – Talimogene laherparepvec/T-VEC
Vemurafenib

- Selective BRAF kinase inhibitor (V600E mutation)
  \[ ve = V600E \]
  \[ mu = \text{mutation} \]
  \[ rafenib = \text{RAF inhibitor} \]

- Approved for treatment of unresectable or metastatic melanoma with BRAF^{V600E} mutation - August 2011

Flaherty et al. New Engl J Med. 2010
BRAF mutation

• 50-60% of all melanomas harbor mutations at codon 600
  – Valine (V) to glutamic acid (E) substitution most common mutation at position 600 = V600E (90%)
  – 2\textsuperscript{nd} most common mutation is V600K (valine $\rightarrow$ lysine)
  – Mutation results in constitutive activation of the MAP kinase signaling pathway = dysregulated tumor growth

• V600E/K mutations confer increased sensitivity to BRAF inhibitors (vemurafenib, dabrafenib)
a

Growth factor

Receptor

RAS

RAF

Vemurafenib

MEK

ERK

Gene expression

Proliferation, cell survival, angiogenesis

b

Vemurafenib

Propane-1-sulfonic acid (3-{5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl-2,4-difluorophenyl})-amide: C_{25}H_{28}ClF_{2}N_{4}O_{3}S; M_w = 489.9
Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antonio Ribas, M.D.,
Grant A. McArthur, M.B., B.S., Ph.D., Jeffery A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D.,
Joseph F. Grippi, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D.,
John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D.,
Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D.,
Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D.,
Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D.,
Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffery A. Sosman, M.D.,
John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D.,
Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A.,
Jeanie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D.,
and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group™
Vemurafenib

• Up to 80% of patients with the BRAF V600E mutation will have at least a partial response within weeks

• The majority of patients will experience relapse
  – Secondary mutations develop within melanomas in response to therapy
  – Median time to progression: 6-7 months
  – Few long term responders
How is BRAF testing performed?

• PCR-based BRAF V600 mutation test
  – Used on formalin-fixed, paraffin-embedded tissue, so biopsy specimens sent for routine histopathology are used
  – Sensitive detection of the BRAF V600E mutation
  – May also detect other mutations such as V600D, V600K, V600R
### Additional options for BRAF testing

- **Targeted next generation sequencing panels**
  - Ability to assay for mutations in multiple oncogenes
  - Used on formalin-fixed, paraffin-embedded tissue

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<table>
<thead>
<tr>
<th>Gene 1</th>
<th>Gene 2</th>
<th>Gene 3</th>
<th>Gene 4</th>
<th>Gene 5</th>
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<td>ARAF</td>
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<td>GNAQ</td>
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<td>KDM5C</td>
<td>KDM6A</td>
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<td>KRAS</td>
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<td>MED12</td>
<td>MEN1</td>
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<tr>
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</table>

[http://www.pennmedicine.org/personalized-diagnostics/services.html](http://www.pennmedicine.org/personalized-diagnostics/services.html)
Vemurafenib

• Side effects
  – 40% of patients require dose reduction
  – Systemic manifestations
    • Fatigue, arthralgias are common
Vemurafenib

• Side effects
  – Skin
    • SCCs and keratoacanthomas in 15-30%
    • New melanomas, atypical nevi
    • Photosensitivity
    • Lobular panniculitis
    • Acneiform eruption/folliculitis

– Some of the cutaneous side effects caused by paradoxical activation of the MAPK signaling pathway in cells harboring wild type (non-mutated) BRAF

Flaherty et al. New Engl J Med. 2010
Other targeted therapy agents

- Da**BRAF**enib/Enco**RAF**enib
  - BRAF inhibitor
  - Similar response rates to vemurafenib

- Tra**ME**tinib/Cobi**ME**tinib/Bini**ME**tinib
  - MEK inhibitors
  - Side effect profile is different (hypertension, decreased EF, transient retinopathy)
Combination BRAFi + MEKi superior to single agent BRAFi

Robert et al, NEJM 2015
Combination therapy is now preferred over monotherapy

• BRAF/MEK combination therapy
  – Dabrafenib/Trametinib
  – Vemurafenib/Cobimetinib
  – Encorafenib/ Binimetinib

  – Regimens are similar to one another
  – Are more effective than single agent therapy

Combination therapy therefore preferred, unless there are contraindications
Decreased #’s of SCCs and KAs with vemurafenib and cobimetinib treatment compared to vemurafenib + placebo

**Table 3. Common Adverse Events.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Vemurafenib and Placebo (N=219)</th>
<th>Vemurafenib and Cobimetinib (N=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>21 (9)</td>
<td>70 (29)</td>
</tr>
<tr>
<td>Most common adverse events†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51 (21)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (18)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (9)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Rash</td>
<td>46 (19)</td>
<td>27 (11)</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>25 (10)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>49 (21)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42 (18)</td>
<td>24 (10)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>43 (18)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>53 (22)</td>
<td>31 (13)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>55 (23)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>17 (7)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Increased aspartate amino-</td>
<td>15 (6)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Increased creatine kinase</td>
<td>6 (3)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

The safety population was analyzed according to the study treatment received. Eight patients assigned to the control group received investigational cobimetinib as a result of dispensing errors. Two patients (one in each study group) did not receive the assigned study drug and were therefore excluded from the analysis. Multiple occurrences of a specific adverse event for a patient were counted once at the highest grade of the occurrence, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. For example, if a patient had two episodes of a specific toxic event, one grade 3 and one grade 4, the patient was counted only once in the grade 4 column. Similarly, in the “Any adverse events” row, if a patient had, for example, three separate events of grade 1, 3, and 4, the patient was counted only once in the grade 4 column.

† The most common adverse events were those that occurred in at least 20% of the patients in either study group.
FDA approved medications for advanced melanoma

• Targeted kinase inhibitors
  – BRAF inhibitors (vemurafenib, dabrafenib, encorafenib)
  – MEK (trametinib, cobimetinib, binimetinib)

• Immunotherapy agents
  – Ipilimumab
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Ipilimumab

- Cytotoxic T-lymphocyte antigen-4 antibody
  - Enhances immune response/antitumor activity
  - Inhibit CTLA-4, which is a negative regulator of T-cell activation
Ipilimumab

- 4 IV doses, 3 weeks apart
  - Effect often seen towards the end of dosing
  - 10 – 15% of patients will respond
  - But many of these patients will have durable response
Ipilimumab

• Toxic side effects
  – General activation of immune system, leading to immune-related issues
    • Diarrhea/colicitis, hepatitis
    • Hypophysitis
    • Skin manifestations
      – Morbilliform eruption
      – Pruritus
      – Vitiligo

Hodi et al, NEJM, 2010
Pseudoprogression and Immune-Related Response in Solid Tumors

Victoria L. Chiou and Mauricio Burotto, Center for Cancer Research, National Cancer Institute, Bethesda, MD

- Some experience initial increase in radiologic tumor size → bx shows inflammatory cell infiltrate → subsequent decreased tumor burden
- Need to distinguish pseudoprogression from actual progression of disease

Chiou et al, J Clin Oncology 2015
Di Giacomo et al., Cancer Immunol Immunother 2009
• Programmed cell death-1 antibodies
  – Enhances immune response/antitumor activity
  – Inhibit PD-1, which plays an important role in downregulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance
Nivolumab and Pembrolizumab

- IV dosing, indefinitely (?)
- Higher response rate than ipilimumab
  - 30% will have objective response
- More rapid response
- Fewer side effects
  - 10% discontinued pembrolizumab in clinical trials
Can predictive biomarkers help predict who will respond to PD-1 inhibitors?

• PD-L1 expression
• Tumor infiltrating lymphocytes
• Other immune regulatory molecules
• Baseline tumor size
  – Smaller baseline tumor size is prognostic of survival and predictive of response with pembrolizumab

Joseph et al, ASCO 2014
Are two drugs better than one?

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma


Larkin et al., NEJM 2015
Combination nivolumab/ipilimumab is more effective than monotherapy

- Nivolumab
  - PFS: 6.9 months
- Nivolumab + Ipilimumab
  - PFS: 11.5 months
- Ipilimumab
  - PFS: 2.9 months

Larkin et al., NEJM 2015
Progression-free survival according to PD-L1 tumor status

- Among patients with a positive PD-L1 tumor status, median PFS was
  - 14.0 months in the nivolumab group
  - 14.0 months in the nivolumab + ipilimumab group
  - 3.9 months in the ipilimumab group

- Among patients with a negative PD-L1 tumor status, the median PFS was
  - 5.3 months in the nivolumab group
  - 11.2 months in the nivolumab + ipilimumab group
  - 2.8 months in the ipilimumab group

Larkin et al., NEJM 2015
Increased efficacy comes at a cost: more side effects

- 55% grade III/IV adverse events, compared to
  - 16% for nivolumab alone
  - 27% for ipilimumab alone
- 43% had to stop
- 27% did not get 4 cycles of drug
- 3% of patients in original Phase II study died from drugs
How do we decide which medication(s) to use?
<table>
<thead>
<tr>
<th>Targeted Therapy (BRAFi / MEKi)</th>
<th>Immune Therapy (ipilimumab and/or PD-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only works in V600E/K mutations</td>
<td>Anyone</td>
</tr>
<tr>
<td>Higher Likelihood of Response</td>
<td></td>
</tr>
<tr>
<td>Shorter Time to Response</td>
<td></td>
</tr>
<tr>
<td>Long-term benefit is unproven</td>
<td>Long-term response can occur</td>
</tr>
</tbody>
</table>

(courtesy Tara Gangadhar and Ravi Amaravadi)
Summary of NCCN Guidelines
First-line Systemic Therapy

<table>
<thead>
<tr>
<th>BRAF-Mutated</th>
<th>BRAF-Wild-type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred if need early response</strong></td>
<td><strong>Anti–PD-1 monotherapy</strong> (nivolumab or pembrolizumab)</td>
</tr>
<tr>
<td>• BRAF/MEK inhibitor combination (preferred):</td>
<td>• Iplimumab/nivolumab combination</td>
</tr>
<tr>
<td>▪ Dabrafenib/trametinib</td>
<td>• Clinical trial</td>
</tr>
<tr>
<td>▪ Vemurafenib/cobimetinib</td>
<td></td>
</tr>
<tr>
<td>▪ BRAF inhibitor monotherapy (vemurafenib or dabrafenib)</td>
<td></td>
</tr>
<tr>
<td><strong>All other cases</strong></td>
<td></td>
</tr>
<tr>
<td>• Anti–PD-1 monotherapy (nivolumab or pembrolizumab)</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>• Clinical trial</td>
<td></td>
</tr>
</tbody>
</table>

What about ipilimumab monotherapy?

- Higher rates of RFS, OS and distant metastasis-free survival than placebo
  - 5 year RFS:ipi 40.8% versus placebo 30.3%
  - 5 year OS:ipi 65.4% versus placebo 54.4%
  - 5 year DMFS:ipi 48.3% versus placebo 38.9%
- BUT there are more AEs at 10 mg/kg dosing
But new adjuvant options as of 2018…

**Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma**


**ABSTRACT**

**BACKGROUND**

Combination therapy with the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib improved survival in patients with advanced melanoma with BRAF V600 mutations. We sought to determine whether adjuvant dabrafenib plus trametinib would improve outcomes in patients with resected, stage III melanomas with BRAF V600 mutations.

**METHODS**

In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 820 patients with completely resected, stage III melanoma with BRAF V600E or V600K mutations to receive oral dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg once daily (combination therapy; 486 patients) or two matched placebo tablets (434 patients) for 12 months. The primary end point was relapse-free survival. Secondary end points included overall survival, distant metastasis-free survival, freedom from relapse, and safety.

**RESULTS**

At a median follow-up of 2.9 years, the estimated 3-year rate of relapse-free survival was 58% in the combination-therapy group and 39% in the placebo group (hazard ratio for relapse or death, 0.6; 95% confidence interval [0.57, 0.67]; P<0.001). The 3-year overall survival rate was 86% in the combination-therapy group and 77% in the placebo group (hazard ratio for death, 0.57; 95% CI, 0.42 to 0.70; P<0.0001), but this level of improvement did not cross the prespecified interim analysis boundary of P=0.00601. Rates of distant metastasis-free survival and freedom from relapse were also higher in the combination-therapy group than in the placebo group. The safety profile of dabrafenib plus trametinib was consistent with that observed with the combination in patients with metastatic melanoma.
And now in 2019...

- FDA approved pembrolizumab for adjuvant treatment of resected Stage IIIA, IIIB, and IIIC melanoma on February 19, 2019
FDA approved medications for advanced melanoma

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  – Talimogene laherparepvec/T-VEC
Talimogene Laherparepvec (T-VEC)

- Approved by the FDA in October 2015 for treatment of unresectable Stage IIIB, IIIC, or IV melanoma
- First in class oncolytic virus based on modified HSV-1
  - Injectable therapy, directed into tumor tissue
  - Modified via deletion of 2 nonessential viral genes
- Designed to selectively replicate in and lyse tumor cells while promoting regional and systemic antitumor immunity
  - Should not harm normal tissue
**T-VEC = engineered HSV-1**

<table>
<thead>
<tr>
<th>Genetic modification</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>deletion of ICP34.5</td>
<td>prevents HSV infection of non-tumor cells, providing tumor-selective replication</td>
</tr>
<tr>
<td>deletion of ICP47</td>
<td>enables antigen presentation</td>
</tr>
<tr>
<td>insertion of human GM-CSF gene (behind CMV promoter)</td>
<td>enhances anti-tumor immune response by recruiting and stimulating dendritic cells to tumor site</td>
</tr>
</tbody>
</table>
Proposed mechanism of action of T-VEC

- T-VEC selectively replicates in tumor cells and lysed them → release of progeny virus and tumor-derived antigens (TDAs)
- T-VEC modified to include 2 copies of human GM-CSF → promotes maturation and function of dendritic cells → activate anti-tumor T-cells through presentation of processed TDAs

Harrington et al, 2015
Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma


See accompanying article on page 2812

Purpose
Talimogene laherparepvec (T-VEC) is a herpes simplex virus type 1–derived oncolytic immunotherapy designed to selectively replicate within tumors and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumor immune responses. T-VEC was compared with GM-CSF in patients with unresected stage IIIB to IV melanoma in a randomized open-label phase III trial.

Patients and Methods
Patients with injectable melanoma that was not surgically resectable were randomly assigned at a two-to-one ratio to intralesional T-VEC or subcutaneous GM-CSF. The primary end point was durable response rate (DRR; objective response lasting continuously ≥ 6 months) per independent assessment. Key secondary end points included overall survival (OS) and overall response rate.

Results
Among 436 patients randomly assigned, DRR was significantly higher with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%); odds ratio, 8.9; P < .001). Overall response rate was also higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% v 6.7%; 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P = .051). T-VEC efficacy was most pronounced in patients with stage IIIIB, IIC, or IVMi1a disease and in patients with treatment-naive disease. The most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia. The only grade 3 or 4 AE occurring in ≥ 2% of T-VEC–treated patients was cellulitis (2.1%). No fatal treatment-related AEs occurred.

Conclusion
T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase III clinical trial. T-VEC was well tolerated and resulted in a higher DRR (P < .001) and longer median OS (P = .051), particularly in untreated patients or those with stage IIIIB, IIC, or IVMi1a disease. T-VEC represents a novel potential therapy for patients with metastatic melanoma.

- 78 patients in T-VEC arm showed response, 56/78 were ongoing at time of end point assessment
- 8 pts in GM-CSF arms responded
Penn Multidisciplinary Melanoma Program

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