MELANOMA—TODAY AND TOMORROW

Kim-Margolin, M.D.
City of Hope

Las Vegas 11/13/16
Disclosures

- Consulting
  - ImaginAb
  - Pfizer
  - Spectrum
  - Prometheus

- Research support (to institution)
  - Merck
  - Altor
  - Amgen
  - BMS
TOPICS TO BE COVERED

- Molecular pathogenesis—emerging concepts of a heterogeneous cancer
  - Cutaneous subtypes
  - Acral
  - Mucosal
  - Uveal

- Local therapies—we will not cover surgery, radiotherapy or adjuvant therapy in detail

- Advanced melanoma—so much progress in so little time!
  - Molecularly-targeted
  - Immunotherapy
  - Cross-modality concepts
  - Brain metastases
40’ for >1-h talk (50’ talk if run a little)
State of the field—adjuvant Rx

- IFN-α has had its day
  - Minute improvements in survival
  - Unfavorable therapeutic index

- Ipilimumab has shown the same RFS benefit (N=951)
  - HR .75 vs placebo
  - Higher dose than in advanced disease—10 mg/kg
  - Longer duration than in advanced disease—4x at 3-wk intervals, then q 12 wks up to 3 yr
  - OS benefit pending longer f/u, may be challenging with better Rxs

- Ipi 3 vs ipi 10 vs IFN-α completed, results not reported
Current U.S. adjuvant study

- Pts with at least N1a > 1 mm nodal disease OR resected mets except brain
- Randomization to pembro—2 mg/kg q 3 wk x 1 yr or choice of IFN-α or ipilimumab standard regimens
- Extensive immune and molecular correlates planned
Primary Endpoint: Recurrence-free Survival (IRC)

<table>
<thead>
<tr>
<th></th>
<th>Ipi</th>
<th>Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>234/475</td>
<td>294/476</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.75 (0.64–0.90)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value*</td>
<td>0.0013</td>
<td></td>
</tr>
<tr>
<td>2-Year RFS rate (%)</td>
<td>51.5</td>
<td>43.8</td>
</tr>
<tr>
<td>3-Year RFS rate (%)**</td>
<td>46.5</td>
<td>34.8</td>
</tr>
</tbody>
</table>

*Stratified by stage.
**Data are not yet mature.

I changed "relapse" with "recurrence"

Stefan Suciu, 9/15/2014
Subgroup Analyses of RFS: Microscopic (N1) vs Clinically Palpable (N2) Lymph Nodes

**Interferon (IFN)/PEG-IFN**
EORTC 18952/EORTC 18991

- IIIB/III-N1: IFN/PEG-IFN
- III-N2: IFN/PEG-IFN
- IIIB/III-N1: Observation
- III-N2: Observation

**Ipi**
EORTC 18071

- III-N1: Ipi
- III-N2: Ipi
- IIIB/III-N1: Observation
- III-N2: Observation

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**Stage IIIB/III-N1:** 
HR 0.78 (99% CI: 0.61–0.99)

**Stage III-N2:** 
HR 0.91 (99% CI: 0.74–1.12)

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**Stage III-N1:** 
HR 0.68 (99% CI: 0.47–0.99)

**Stage III-N2:** 
HR 0.83 (99% CI: 0.63–1.0)

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### Safety: Immune-related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Ipi (n=471)</th>
<th>Pbo (n=474)</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Any irAE</td>
<td>90.4</td>
<td>36.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>63.3</td>
<td>4.5</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>34.4</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>46.3</td>
<td>14.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41.4</td>
<td>9.6</td>
<td>0</td>
</tr>
<tr>
<td>Colitis*</td>
<td>15.9</td>
<td>6.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Endocrine</td>
<td>37.6</td>
<td>7.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>18.3</td>
<td>4.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.9</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>25.1</td>
<td>7.9</td>
<td>2.8</td>
</tr>
<tr>
<td>LFT increase</td>
<td>19.7</td>
<td>3.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Neurologic</td>
<td>4.5</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Other</td>
<td>23.6</td>
<td>7.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

LFT = liver function test. *Gastrointestinal perforations: Ipi, 6 related (1.3%); Pbo, 3 unrelated (0.6%).

Eggermont et al Lancet Oncology 2015
Time to Onset of Grade 2-5 irAEs

- **Skin**
  - Median time to onset (ipilimumab): 4.3 wks (range: 0.3–144.1)

- **Gastrointestinal**
  - Median time to onset (ipilimumab): 6.3 wks (range: 0.3–145.0)

- **Hepatic**
  - Median time to onset (ipilimumab): 8.7 wks (range: 1.9–48.0)

- **Endocrine**
  - Median time to onset (ipilimumab): 10.8 wks (range: 0.3–90.1)
Advanced melanoma—still a force to be reckoned with

- **Challenges**
  - Insufficient percentage of patients benefit from immuno- and molecular therapies
  - De novo resistance and escape from initial control remain difficult to predict and overcome
  - Subsets of disease have less-favorable outcomes, especially uveal

- **Recent insights leading to new strategies**
  - PD-L1 and related immunomodulatory molecules
  - Interactions between driver oncogenes and immune response
  - Mutational burden and antigen discovery
Ipilimumab in advanced melanoma:
pooled OS, including EAP data; \( N = 4846 \)

Median OS, months (95% CI): 9.5 (9.0–10.0)

3-year OS rate, % (95% CI): 21 (20–22)
Pembrolizumab in advanced Melanoma active independent of ipi-exposure

In patients with measurable disease at baseline by RECIST v1.1 by central review and ≥1 postbaseline assessment (n = 317). Percentage changes >100% were truncated at 100%.

Analysis cut-off date: October 18, 2013.
**Pembrolizumab in advanced melanoma**

Efficacy both in PDL1 + and - pts

*Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per central review and ≥1 postbaseline tumor assessment.
Percentage changes >100% truncated at 100%.
PD-L1 positivity defined as staining in ≥1% of tumor cells.
Analysis cut-off date: 18 October 2013.

1. Daud A et al. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA.
PFS and OS based on tumor PD-L1 expression

Progression-Free Survival

Overall Survival

PD-L1 positivity defined as staining in ≥1% of tumor cells.
Analysis cut-off date: 18 October 2013.
1. Daud A et al. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA.
Anti PD1 (nivolumab) in BRAFwt

Hazard ratio for death, 0.42 (99.79% CI, 0.25–0.73)
P<0.001

Patients Who Died
No./Total no.
Nivolumab 50/210
Dacarbazine 96/208

Median Survival
Mo (95% CI)
Nivolumab Not reached 10.8 (9.3–12.1)
Dacarbazine

No. at Risk
Nivolumab 210 185 150 105 45 8 0
Dacarbazine 208 177 123 82 22 3 0

Robert et al, NEJM 2015
Pembrolizumab vs Ipilimumab—PFS

Robert et al NEJM 2015
Phase III study of pembrolizumab (10 mg/kg Q2W or Q3W) vs ipilimumab

CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone

Unresectable or Metastatic Melanoma
• Previously untreated
• 945 patients

Randomize 1:1:1

Stratify by:
• Tumor PD-L1 expression*
• BRAF mutation status
• AJCC M stage

N=314

NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316

NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315

IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Treat until progression** or unacceptable toxicity

*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.
Progression-Free Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro Q2W</td>
<td>181</td>
<td>0.61 (0.50-0.75)</td>
<td>&lt;0.0000</td>
</tr>
<tr>
<td>Pembro Q3W</td>
<td>183</td>
<td>0.61 (0.50-0.75)</td>
<td>&lt;0.0000</td>
</tr>
<tr>
<td>Ipi</td>
<td>202</td>
<td>31% (28%-31%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

P values are nominal only because no statistical alpha was applied to the comparison at final analysis.

Final analysis data cutoff date: Dec 3, 2015.

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Assessed per RECIST v1.1 by independent central review.
**PFS by PD-L1 expression (5%)**

**Ipilimumab vs Nivolumab vs combo**

**PD-L1 ≥5%**

- **mPFS**
  - NIVO + IPI: 14.0
  - NIVO: 14.0
  - IPI: 2.9

- **HR**
  - NIVO + IPI: 0.4
  - NIVO: 0.4
  - IPI: --

**PD-L1 <5%**

- **mPFS**
  - NIVO + IPI: 11.2
  - NIVO: 5.3
  - IPI: 2.8

- **HR**
  - NIVO + IPI: 0.4
  - NIVO: 0.6
  - IPI: --

**No. at Risk**

- **NIVO + IPI**
  - Month 0: 68
  - Month 17: 1

- **NIVO**
  - Month 0: 208
  - Month 17: 5

- **IPI**
  - Month 0: 75
  - Month 17: 1

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.*
## Response to treatment

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>57.6 (52.0–63.2)</td>
<td>43.7 (38.1–49.3)</td>
<td>19.0 (14.9–23.8)</td>
</tr>
<tr>
<td>Two-sided P value vs IPI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td><strong>Best overall response — %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>12.1</td>
<td>9.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>45.5</td>
<td>33.9</td>
<td>16.8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13.1</td>
<td>10.4</td>
<td>21.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22.6</td>
<td>38.0</td>
<td>48.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.7</td>
<td>7.9</td>
<td>10.2</td>
</tr>
<tr>
<td><strong>Median duration of response, months (95% CI)</strong></td>
<td>NR (20.5–NR)</td>
<td>22.3 (20.7–NR)</td>
<td>14.4 (8.3–NR)</td>
</tr>
<tr>
<td><strong>Ongoing response among responders, %</strong></td>
<td>72.5</td>
<td>72.4</td>
<td>51.7</td>
</tr>
</tbody>
</table>

*By RECIST v1.1. NR = not reached.

Larkin et al NEJM 2015
**PFS by PD-L1 expression level (5%)**

<table>
<thead>
<tr>
<th>PD-L1 ≥5%*</th>
<th>mPFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>14.0</td>
<td>0.40</td>
</tr>
<tr>
<td>NIVO</td>
<td>14.0</td>
<td>0.40</td>
</tr>
<tr>
<td>IPI</td>
<td>3.9</td>
<td>--</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1 &lt;5%*</th>
<th>mPFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>11.2</td>
<td>0.42</td>
</tr>
<tr>
<td>NIVO</td>
<td>5.3</td>
<td>0.60</td>
</tr>
<tr>
<td>IPI</td>
<td>2.8</td>
<td>--</td>
</tr>
</tbody>
</table>

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

Larkin et al NEJM 2015
Response by tumor PD-L1 expression*

<table>
<thead>
<tr>
<th>PD-L1 (≥5%)</th>
<th>ORR, % (95% CI)</th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>72.1 (59.9–82.3)</td>
<td>57.5 (45.9–68.5)</td>
<td>21.3 (12.7–32.3)</td>
<td></td>
</tr>
<tr>
<td>Median Duration of Response (months)</td>
<td>NR</td>
<td>20.7</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1 (&lt;5%)</th>
<th>ORR, % (95% CI)</th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>54.8 (47.8–61.6)</td>
<td>41.3 (34.6–48.4)</td>
<td>17.8 (12.8–23.8)</td>
<td></td>
</tr>
<tr>
<td>Median Duration of Response (months)</td>
<td>NR</td>
<td>22.3</td>
<td>18.2</td>
<td></td>
</tr>
</tbody>
</table>

*Pre-treatment tumor specimens were centrally assessed by IHC (using a validated BMS/Dako assay) for PD-L1.

Larkin et al NEJM 2015
<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
</tr>
<tr>
<td><strong>Skin AEs, %</strong></td>
<td>60.4</td>
<td>5.8</td>
<td>43.8</td>
</tr>
<tr>
<td>Rash</td>
<td>28.4</td>
<td>2.9</td>
<td>22.7</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35.1</td>
<td>1.9</td>
<td>20.4</td>
</tr>
<tr>
<td><strong>Gastrointestinal AEs, %</strong></td>
<td>47.6</td>
<td>15.3</td>
<td>21.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45.4</td>
<td>9.6</td>
<td>20.8</td>
</tr>
<tr>
<td>Colitis</td>
<td>11.5</td>
<td>8.0</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Endocrine AEs, %</strong></td>
<td>32.3</td>
<td>5.8</td>
<td>15.7</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16.0</td>
<td>0.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10.2</td>
<td>1.0</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Hepatic AEs, %</strong></td>
<td>31.6</td>
<td>19.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>17.9</td>
<td>8.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>15.7</td>
<td>6.1</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Pulmonary AEs, %</strong></td>
<td>7.3</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6.7</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Renal AEs, %</td>
<td>6.4</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>4.2</td>
<td>0.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Immune mediated AEs in the vast majority (>85%) of patients.

Larkin et al NEJM 2015

Database lock Nov 2015
Toxicities of (CTLA-4+PD-1) blockade

- irAE can be severe, but manageable with standard immunosuppressive Rxs
- Similar across age, disease characteristics
  - 30-40% led to treatment discontinuation
  - Majority occurred within first 12 weeks
  - 80% AE resolved with immunosuppression
  - Endocrinopathies tend to be permanent but easily managed
  - Few treatment related deaths (069 = 3, 067 = 0)
- Toxicity did not interfere with response
- Immunosuppression for toxicity did not prevent or curtail ongoing therapeutic benefit
Co-localization of PD-L1 expression and infiltrating CD 8 cells in melanoma

Data provided by Lieping Chen (Yale University), Janice Taube (JHU)

T cell \rightarrow Cytokines (IFN \gamma)

PD-L1/PD1 interaction inhibits T-cell function

Induction of tumor and immune cell PD-L1
*"DRIVER" MUTATIONS*

- **GNAQ 32%**
  - G11 45%
  - BAP1 bad
  - SF3B1 good

- **NRAS 15%**
  - BRAF 28%
  - Scalp/Face
  - C-Kit 5%-10%
  - NRAS 25%
  - BRAF 10%
  - Acral
  - C-Kit 10%-20%
  - NRAS 15%
  - Mucosal

- **NRAS 18%**
  - BRAF 57%
  - Trunk/Legs

*(add NF1; "passengers" also critically important)*

**References**
- Van Ramsdonk et al. N Engl J Med 2010 Dec 2;363
Constitutive activation of tyrosine kinase receptors (TKR)
c-Kit mutation in approximately ±20% of lentiginous melanomas
Amplification of c-kit, EGFR-γ, PDGFR-α,

Mutation in 15%-30% of melanomas
(particularly on skin without chronic sun-induced damage)

Mutation in 30%-70% of melanomas
(particularly on skin without chronic sun-induced damage)

Amplification (uncommon mutation)

Loss in 20%-50% of melanomas due to mutation/deletion/silencing

Overexpression in 80% of melanomas

Loss in 30%-70% of melanomas due to mutation/deletion/silencing

Amplification (common in lentiginous melanomas)
Landscape of melanoma driver mutations

Hodis et al Cell 2012
Figure 6.
Landscape of Driver Mutations in Melanoma
(A) Per-sample mutation rate (top). Color-coded matrix of individual mutations and copy number alterations (middle). In cases in which multiple mutations per gene were found in a sample, only one mutation is shown, with preference given to LoF (nonsense/splice/frameshift) mutations and then hot spot/COSMIC-recurrent mutations. Final row indicates primary origin of melanoma. Mutation spectra of all samples (bottom).
(B) Distribution of selected mutations and copy number amplifications in \textit{BRAF}, \textit{NRAS}, \textit{NF1}, \textit{HRAS}, \textit{RAF1}, \textit{MAP2K1}, \textit{KIT}, \textit{GNA11}, \textit{CCND1}, and \textit{CDK4} are shown across all samples.
MAP kinase-targeted therapy: the triumph and the tragedy

Resistance

Courtesy, G. Long
Dabrafenib + Trametinib vs Dab: Rationale

**BRAFi (dabrafenib)**
- PFS HR, 0.37 vs DTIC\(^1\)
- Hyperproliferative skin AEs

**BRAFi (vemurafenib)**
- PFS HR, 0.38 vs DTIC\(^2\)
- Hyperproliferative skin AEs

**MEKi (trametinib)**
- PFS HR, 0.45 vs chemotherapy\(^3\)

**BRAFi + MEKi ph 3 studies**

**Dabrafenib + trametinib**
- PFS HR, 0.67 vs dabrafenib\(^4\)
- OS HR, 0.71 vs dabrafenib\(^4\)

**Vemurafenib + cobimetinib**
- PFS HR, 0.58 vs vemurafenib\(^6\)
- OS HR, 0.70 vs vemurafenib\(^6\)

Decreased hyperproliferative skin AEs\(^4,5,6\)

---


Presented by: Keith T. Flaherty, MD
COMBI-D: PFS and OS\textsuperscript{a}

58\% of D+T patients alive at 3 years still on D+T

Progression-Free Survival

Overall Survival

Dabrafenib + Trametinib (n = 211)

Dabrafenib + Placebo (n = 212)

Number at risk

\begin{align*}
\text{D+T} & : 211 & 137 & 84 & 69 & 54 & 45 & 31 & 0 \\
\text{D+Pbo} & : 212 & 110 & 67 & 41 & 29 & 11 & 7 & 1 & 0 \\
\end{align*}

a Intent-to-treat population; b Dabrafenib + placebo includes 26 patients who crossed over to combination arm; +, censored.
COMBI-D: Elevated LDH

**PFS**

- **Dabrafenib + Trametinib (n = 76)**
  - 2-y PFS, 17%
  - 3-y PFS, 13%
- **Dabrafenib + Placebo (n = 71)**
  - 2-y PFS, 8%
  - 3-y PFS, 4%

**OS**

- **Dabrafenib + Trametinib (n = 76)**
  - 2-y OS, 27%
  - 3-y OS, 25%
- **Dabrafenib + Placebo (n = 71)**
  - 2-y OS, 17%
  - 3-y OS, 14%

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>D+T</th>
<th>D+Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0-6</td>
<td>76</td>
<td>71</td>
</tr>
<tr>
<td>6-12</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>12-18</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>18-24</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>24-30</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>30-36</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>36-42</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>42-48</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

+, censored.
COMBI-D: Normal LDH

PFS

Dabrafenib + Trametinib (n = 133)

2-y PFS, 37%
3-yr PFS, 27%

Dabrafenib + Placebo (n = 140)

2-y PFS, 21%
3-yr PFS, 17%

OS

Dabrafenib + Trametinib (n = 133)

2-y OS, 65%
3-y OS, 54%

Dabrafenib + Placebo (n = 140)

2-y OS, 55%
3-y OS, 41%

Number at risk

D+T  133  96  67  57  44  36  24  0
D+Pbo 140  90  55  34  24  7   5   1

+, censored.
COMBI-D: Normal LDH\(^a\) and < 3 Disease Sites\(^b\)

**PFS**

- **Dabrafenib + Trametinib (n = 76)**
  - 3-y PFS, 38%

- **Dabrafenib + Placebo (n = 96)**
  - 3-y PFS, 15%

**OS**

- **Dabrafenib + Trametinib (n = 76)**
  - 2-y OS, 68%
  - 3-y OS, 62%

- **Dabrafenib + Placebo (n = 96)**
  - 2-y OS, 61%
  - 3-y OS, 45%

---

\(^a\) Baseline LDH ≤ ULN; \(^b\) Any organ at baseline with ≥ 1 metastasis could be counted as a single disease site; +, censored.
Co-BRIM Overall Survival

HR (95% CI) 0.65 (0.42-1.00)
P value two-sided 0.046

No. at Risk
Vemurafenib + cobimetinib (n = 247) 243 229 182 112 62 20 6
Vemurafenib + placebo (n = 248) 245 227 166 101 53 21 2

CI, confidence interval; NE, not estimable.

Slide Courtesy Grant McArthur
Combi-V Overall Survival

Adjusted HR (95% CI) 0.69 (0.53-0.89)
2-sided P-value (stopping boundary) 0.005 (<0.0214)

D + T, dabrafenib + trametinib; Vem, vemurafenib

Robert et al. NEJM, 2015
Molecular mechanisms of resistance

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Mechanism of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTKs upregulation</td>
<td>RTK activation can signal either through CRAF or through the PI3K pathway</td>
</tr>
<tr>
<td>Mutations in NRAS</td>
<td>NRAS-activating mutations (NRAS&lt;sup&gt;Q61&lt;/sup&gt;, NRAS&lt;sup&gt;T58&lt;/sup&gt;, NRAS&lt;sup&gt;G138&lt;/sup&gt;) promote enhanced RAF dimerization; RAF inhibitors binding of one member of the dimer results in allosteric transactivation of the drug-free protomer and activation of MEK/ERK</td>
</tr>
<tr>
<td>Activating MEK1/2 mutations</td>
<td>MEK1 is situated immediately downstream of RAF proteins in the MAPK pathway and promotes ERK phosphorylation; MEK2 forms heterodimers with MEK1 which activate ERK. Only some mutations have been associated with resistance (MEK1&lt;sup&gt;C121S&lt;/sup&gt;, MEK1&lt;sup&gt;Q56P&lt;/sup&gt;, MEK1&lt;sup&gt;K57E&lt;/sup&gt;, MEK1&lt;sup&gt;E203K&lt;/sup&gt;, MEK1&lt;sup&gt;V60E&lt;/sup&gt;, MEK1&lt;sup&gt;G128V&lt;/sup&gt;, MEK2&lt;sup&gt;Q57C&lt;/sup&gt;, MEK2&lt;sup&gt;C125S&lt;/sup&gt;, MEK2&lt;sup&gt;V35M&lt;/sup&gt;, MEK2&lt;sup&gt;L46R&lt;/sup&gt;, MEK2&lt;sup&gt;N126D&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Alternative splicing of V600E BRAF</td>
<td>Owing to high dimerization property irrespective of RAS status, strongly activates MEK and ERK1/2 in the presence of an RAF inhibitor</td>
</tr>
<tr>
<td>V600E BRAF copy number amplification</td>
<td>MEK/ERK reactivation in an RAS and CRAF-independent manner due to an increased expression of BRAF</td>
</tr>
<tr>
<td>Elevated CRAF</td>
<td>Elevated CRAF protein levels have been associated with increased levels of phosphorylated ERK1/2 levels and may account for the acquisition of resistance to BRAFi due to increased RAF dimerization</td>
</tr>
<tr>
<td>Alterations of PI3K-AKT pathway</td>
<td>AKT1/3 mutations (Q79K and E17K), mutations in PI3K–AKT positive-regulatory genes (PIK3CA and PIK3CG) and in negative-regulatory genes (PIK3R2 and PHLPP1) upregulate the PI3K-AKT pathway; the missense mutation AKT1&lt;sup&gt;A102V&lt;/sup&gt; has not been associated with AKT1 activation.</td>
</tr>
</tbody>
</table>
Next steps for MAP kinase inhibitors

Doublet therapy: BRAFi and MEKi

Optimal schedule to prolong benefit?

Upfront triple therapy
BRAFi + MEKi + Drug X

Drug X at progression
BRAFi + MEKi → Drug X

PI3K/ mTOR/AKT
VEGF
CDK 4/6
C-Met
bFGF
First-line Rx for BRAF mutant advanced melanoma? EA6134 Ipi/Nivo to D/T vs D/T to Ipi/Nivo

Arm 1:
- Ipi 3/Nivo 1 mg/kg/ q 3wks x 4
- Plus Maint Nivo
- Dabrafenib 150 mg bid
- Trametinib 2 mg/day

Arm 2:
- Ipi 3/Nivo 1 mg/kg
- q 3wks x 4
- Plus Maint Nivo

PD

Randomize

ECOG PS
1. 0
2. 1

LDH
1. Normal
2. Elevated
T-VEC: HSV-1-derived intratumoral therapy for local and systemic effects

Local Effect: Tumor Cell Lysis
- Healthy cells
- Cancer cells
- Selective viral replication in tumor tissue
- Tumor cells rupture for an oncolytic effect

Systemic Effect: Tumor-Specific Immune Response
- Tumor-specific immune response
- Death of distant cancer cells

T-VEC key genetic modifications:
- JS1/ICP34.5-/-ICP47-/-hGM-CSF

Courtesy of Howard Kaufman
## TVEC overall response rate

<table>
<thead>
<tr>
<th>ITT Set</th>
<th>GM-CSF (N=141)</th>
<th>T-VEC (N= 295)</th>
<th>Treatment Difference (T-VEC – GM-CSF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate (95% CI)</td>
<td>5.7% (1.9, 9.5)</td>
<td>26.4% (21.4, 31.5)</td>
<td>20.8% (14.4, 27.1) P &lt; 0.0001&lt;sup&gt;a&lt;/sup&gt; descriptive</td>
</tr>
<tr>
<td>CR</td>
<td>0.7%</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>5.0%</td>
<td>15.6%</td>
<td></td>
</tr>
</tbody>
</table>

## Durable response rate (primary endpoint)

<table>
<thead>
<tr>
<th>ITT Set</th>
<th>GM-CSF (N=141)</th>
<th>T-VEC (N= 295)</th>
<th>Treatment Difference (T-VEC – GM-CSF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable Response Rate</td>
<td>2.1%</td>
<td>16.3%</td>
<td>14.1% 95% CI: (8.2, 19.2) P &lt; 0.0001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> descriptive

Andtbacka R et al JCO 2015
Progression-free survival, TVEC vs GM-CSF

T-VEC (N = 295) 163 (55.3%) 8.2 (6.5, 9.9) months
GM-CSF (N = 141) 84 (59.6%) 2.9 (2.8, 4.0) months

Hazard Ratio: 0.42 (0.32, 0.54)
Unadjusted Log-Rank: \( P < 0.0001^* \)
*P-value is descriptive only

Andtbacka R et al JCO 2015
Overall Survival

<table>
<thead>
<tr>
<th>Survival</th>
<th>T-VEC</th>
<th>GM-CSF</th>
<th>Difference % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-mo</td>
<td>73.7%</td>
<td>69.1%</td>
<td>4.6 (-4.7, 13.8)</td>
</tr>
<tr>
<td>24-mo</td>
<td>49.8%</td>
<td>40.3%</td>
<td>9.5 (-0.5, 19.6)</td>
</tr>
<tr>
<td>36-mo</td>
<td>38.6%</td>
<td>30.1%</td>
<td>8.5 (-1.2, 18.1)</td>
</tr>
<tr>
<td>48-mo</td>
<td>32.6%</td>
<td>21.3%</td>
<td>11.3 (1.0, 21.5)</td>
</tr>
</tbody>
</table>

Median (95% CI) in Months

<table>
<thead>
<tr>
<th>Events / N (%)</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-VEC 189 / 295 (64)</td>
<td>23.3 (19.5, 29.6)</td>
</tr>
<tr>
<td>GM-CSF 101 / 141 (72)</td>
<td>18.9 (16.0, 23.7)</td>
</tr>
</tbody>
</table>

HR = 0.79 (95% CI: 0.62, 1.00)
Unadjusted Log-rank $P = 0.051$

Andtbacka R et al JCO 2015
Special case—RT as pleiotropic, *regional* → *systemic* immunomodulator

Animal studies very controllable, convincing; in humans, anecdotal and/or retrospective; prospective randomized studies ongoing w/CTLA4Ab, PD-1 Abs, high-dose IL-2

Demaria, JAMA Oncology 2015
Brain mets: Ipi 10 mg/kg x 4 + maintenance: no steroid or neuro Sx

~26% 2 yr OS also seen in 165-pt cohort from expanded access trial

Margolin et al Lancet Oncology 2012
A multi-center Phase II Open-label Study (CheckMate 204) to Evaluate Safety and Efficacy of Nivolumab (NIVO) in Combination with Ipilimumab Followed by NIVO Monotherapy in Patients with Melanoma Metastatic to the Brain

Kim Margolin,1* Marc S. Ernstoff,2* F. Stephen Hodi,3* David McDermott,4* Robin Edwards,5 Alexandre Avila,5 Michael Atkins5

1Stanford University Medical Center, Stanford, CA, USA; 2Cleveland Clinic Foundation, Cleveland, OH, USA; 3Dana-Farber Cancer Institute; Boston, MA, USA; 4Beth Israel Deaconess Medical Center, Boston, MA, USA; 5Bristol-Myers Squibb, Plainsboro, NJ, USA; 6Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA; 7Cytokine Working Group (CWG)

Background

Brain Metastasis in Melanoma
- Brain metastasis develops in ~50% patients with melanoma
- Progression in the brain is the major cause of melanoma death in patients with brain metastases
- Among these patients, median overall survival (OS) after diagnosis is only 4 months in symptomatic patients
- Successful therapy is limited by low antitumor activity of available agents, relative resistance to radiotherapy and poor CNS penetration of most therapeutic agents
- Immunotherapy has potential in this setting since activated T-cells may cross the blood–brain barrier

Nivolumab (NIVO; Opdivo)
- A fully human IgG4 monoclonal antibody directed against the PD-1 immune checkpoint receptor
- Restores T-cell anti-tumor activity by interfering with the interaction between PD-1 on T cells and PD-1 ligands PD-L1 or PD-L2 on tumor cells (Figure 1)
- Approved in the US for unresectable or metastatic melanoma and disease progression following ipilimumab (IPI; Yervoy) and, if BRAFV600 mutation positive, a BRAF inhibitor
- Approved in Japan for unresectable melanoma

Ipilimumab (IPI)
- A fully human IgG1 monoclonal antibody directed against the CTLA-4 immune checkpoint receptor
- Restores T-cell anti-tumor activity by interfering with the interaction between CTLA-4 on T cells and CD80 and CD86 on antigen-presenting cells (Figure 1)
- Approved for advanced melanoma as first-or subsequent-line treatment
- Activity and survival of melanoma patients with brain metastases treated with IPI similar to that of patients without brain metastases [could add Italian data here]

NIVO plus IPI Combination in Advanced Melanoma
- In a phase 2, double-blind study (CheckMate 869) with treatment-naïve patients with advanced melanoma, combination therapy with NIVO 1 mg/kg plus IPI 3 mg/kg pembrolizumab (n=95) followed by NIVO 3 mg/kg pembrolizumab was associated with manageable safety profile

Study Design

- An open-label, Phase II study of approximately 110 patients with advanced melanoma and measurable brain metastases who may have had prior stereotactic radiotherapy to lesions not used for protocol assessment
- NIVO 1 mg/kg plus IPI 3 mg/kg every 3 weeks (Q3W) for 4 cycles, followed by NIVO 3 mg/kg every 2 weeks (Q2W)
- Assessments:
  - MRI scans of CNS lesions and CT scans of extracranial lesions every 6 weeks for 1 year, then every 12 weeks
  - Log of Quantitative Radiologic Changes in brain index lesions
  - Neurologic assessment, performance status, laboratory tests, safety and tolerability, biomarker analysis

Study Rationale

- NIVO plus IPI followed by NIVO monotherapy will provide clinical benefit to patients with melanoma metastatic to the brain, improving on the results reported with IPI alone

Study Hypothesis

- NIVO plus IPI followed by NIVO monotherapy will provide clinical benefit to patients with melanoma metastatic to the brain, improving on the results reported with IPI alone

Study Objectives

Primary Objective
- Assess the CNS Clinical Benefit Rate (CBR = CR + PR + SD for >6 months) in patients with melanoma metastatic to the brain treated with NIVO plus IPI followed by NIVO monotherapy

Secondary Objectives
- Extracranial CBR
- Global CBR
- Overall survival
- Safety and tolerability

Exploratory Objectives
- Predictive values of biomarkers and pharmacogenomics

Study Sites

27 sites across United States

Inclusion/Exclusion Criteria

Key Inclusion Criteria
- Men and women aged ≥18 years
- Stage III or IV malignant melanoma (regardless of BRAF mutation status) except for uveal primary

RESTRICT-defined disease in one or more extracranial site(s) and modified RESTRICT measurement in one or more brain metastasis 0.5-3 cm in diameter, not counting lesion(s) previously treated with stereotactic radiotherapy
- Allowed prior treatments include chemotherapy, interferon (adjuvant setting), interleukin-2, BRAF/MEK inhibitors, MEK inhibitors, cKIT inhibitors [could shorten this to simply say “any prior Rx allowed except for either study drug”]

Key Exclusion Criteria
- Leptomeningeal metastasis
- Metastases to the brain 0.5 cm or larger in diameter
- Previous radiotherapy

References

Acknowledgments

The contribution of Bristol-Myers Squibb

Professional medical writing assistance was provided by Mark Palangio and professional editing assistance was provided by Karin McGlynn at StemScientific, an Ashfield Company, and was funded by Bristol-Myers Squibb.

*Use of single fraction stereotactic radiotherapy (SRT) allowed for progression of a single CNS lesion

Figure 1. Mechanism of action of combined PD-1 and CTLA-4 blockade

Figure 2. CheckMate 204 Study Design
EA6134: Ipi/Nivo to D/T vs D/T to Ipi/Nivo

**ECOG PS**
- 1. 0
- 2. 1

**LDH**
- 1. Normal
- 2. Elevated

---

**Arm 1:**
Ipi 3/Nivo 1 mg/kg/ q 3wks x 4 +Maint Nivo

**Arm 2:**
D 150 BID / T 2 mg Qd

---

**PD**
Dabrafenib 150 mg bid
Plus Trametinib 2 mg/day

Ipi 3/Nivo 1 mg/kg
q 3wks x 4 + Maint Nivo
Targeted Rx and the immune response (BRAF-mutant melanoma example)

- BRAF-mutated melanoma cells resist immune control, produce more suppressive molecules
- BRAFi Rx enhances MHC and Ag expression, sensitivity to cell-mediated cytotoxicity
- BRAFi Rx increases TCR clonality; expansion of pre-existing clones → favorable outcomes
- Combination MAPKi with BRAFi + MEKi doesn’t diminish T cell function

See editorial by Cooper et al (Wargo) in CCR May, 2015
Radiotherapy: regional ➔ systemic immunomodulator

Animal studies very controllable, convincing; in humans, anecdotal and/or retrospective; prospective randomized studies ongoing w/ CTLA4Ab, PD-1 Abs, high-dose IL-2

Demaria, JAMA Oncology 2015
What is the status of IL-2?

• Survival curves, 1st-line response rates stable
• First-line use in melanoma, RCC vanishing
• ↑ understanding of dynamics, target cell responses but clinical, other predictors still vague
• Preclinical data with checkpoint Abs promising
• New protocols ongoing or in development
  – Lower doses, new forms, support adoptive T cell Rx
  – Various combinations and sequences with CPIs
  – Later-line Rx after CPI failure

NEVER in the NEJM
High-dose IL-2

12% CR

16% PR
Brain mets: Ipi 10 mg/kg x 4 w/ maintenance: OS if no steroid, Sx

~26% 2 yr OS also seen in 165-pt cohort from expanded access trial

Margolin et al Lancet Oncology 2012
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• Approved in Japan for unresectable melanoma.9

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• Approved for advanced melanoma as first-or subsequent-line treatment.12  
• Activity and survival of melanoma patients with brain metastases treated with IP similar to that of patients without brain metastases,13,14 could add Italian data here15

NIVO plus IP Combination in Advanced Melanoma
• In a phase 2, double-blind study (CheckMate 069) with treatment-naïve patients with advanced melanoma, combination therapy with NIVO 1 mg/kg plus IP 3 mg/kg every 3 weeks (Q3W) for 12 cycles, followed by NIVO monotherapy, resulted in manageable safety profile.15  
• Data to be added after publication

Study Design
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• NIVO 1 mg/kg plus IP 3 mg/kg every 3 weeks (Q3W) for 4 cycles, followed by NIVO 3 mg/kg every 2 weeks (Q2W).  
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Key Exclusion Criteria
• Leptomeningeal metastasis  
• Therapeutic corticosteroid or bevazucizumab for symptoms or edema

References

Study Sites
27 sites across United States

Acknowledgments
• To the patients and families for making this trial possible
• To the contribution of Bristol-Myers Squibb
• To professional medical editing
• To SICOS Group and Whitehorn Scientific, an Ashfield Company, and was funded by Bristol-Myers Squibb
And help our patients to live longer and better lives
Survival: Are we at the inflection point?

Progression Free Survival
- Pts, N: 655, 482
- Event Median: 4.9 mo (74%) (3.1-5.5)

Overall Survival
- Pts, N: 655, 358
- Event Median: 24.4 mo (55%) (20.2-29.0)

Assessed per RECIST v1.1 by independent central review.
Excludes patients with ocular melanoma.
Analysis cutoff date: Sep 18, 2015.