Introduction to Melanoma

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Co-Director, Melanoma Program,
University of California, San Francisco

Cancer Mortality Rates by State Economic Area
Melanoma, White Males, 1970-94

1930’s

Now
<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>Acral</th>
<th>Scalp/Face</th>
<th>Trunk/Legs</th>
<th>Uveal</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNAQ 32% G11 45%</td>
<td></td>
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</tr>
<tr>
<td>NRAS 15%</td>
<td></td>
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<tr>
<td>BRAF 57%</td>
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</tr>
<tr>
<td>NRAS 18%</td>
<td></td>
<td></td>
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<tr>
<td>BRAF 28%</td>
<td></td>
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<tr>
<td>C-Kit 10%-20%</td>
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</tr>
<tr>
<td>NRAS 15%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BRAF 10%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C-Kit 5 -10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRAS 25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF 10%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Survival in Melanoma by Stage

Sentinel Node Biopsy

Image courtesy of Douglas Reintgen MD, Moffitt Cancer Center
### Clinical Trials in Metastatic Melanoma-2010

<table>
<thead>
<tr>
<th>Study</th>
<th>Control Arm</th>
<th>Response Rate, %</th>
<th>Study Arm</th>
<th>Response Rate, %</th>
<th>Overall Survival, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 18032</td>
<td>Dacarbazine</td>
<td>9.8</td>
<td>Temozolomide</td>
<td>14.5</td>
<td>9.1 (9.4)</td>
</tr>
<tr>
<td>ECOD 2603 (1st line)</td>
<td>Carbo + Pac</td>
<td>16</td>
<td>Carbo + Pac + Sorafenib</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>PRISM (2nd line)</td>
<td>Carbo + Pac</td>
<td>11</td>
<td>Carbo + Pac + Sorafenib</td>
<td>12</td>
<td>9.8</td>
</tr>
<tr>
<td>Historical NCI-SB &amp; CWG</td>
<td>na</td>
<td>na</td>
<td>High-dose IL-2</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Pfizer 1009 (1st line)</td>
<td>Dacarbazine</td>
<td>10.8</td>
<td>Tremelimumab</td>
<td>9.1</td>
<td>11.2</td>
</tr>
<tr>
<td>MDX010-2 (2nd line)</td>
<td>GP100</td>
<td>1.5</td>
<td>ipilimumab</td>
<td>10.9*</td>
<td>10.0 (6.4)</td>
</tr>
<tr>
<td>Oblimersen Dacarbazine</td>
<td>Dacarbazine</td>
<td>7.5</td>
<td>Dacarbazine + oblimersen</td>
<td>13.5</td>
<td>9.0 (7.8)</td>
</tr>
<tr>
<td>BEAM</td>
<td>Carbo + Pac</td>
<td>16</td>
<td>Carbo + Pac + bevacizumab</td>
<td>18</td>
<td>--</td>
</tr>
</tbody>
</table>


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![Diagram of growth factor pathways and protein translation](image)
Phase III BRIM3 Study design

**Screening**
- BRAF V600E mutation
- Stage
- ECOG PS 0 vs 1
- LDH (↑ vs nl)
- Region

**Randomization**
- N=675

**Vemurafenib**
- 960 mg po bid (N=337)

**Dacarbazine**
- 1000 mg/m² iv q3w (N=338)

**Progression-free survival (February 01, 2012 cut-off) censored at crossover**

- Hazard ratio 0.38 (95% CI: 0.32–0.46)
- Log-rank p<0.001 (post-hoc)
Overall survival (February 01, 2012 cut-off) censored at crossover

Vemurafenib (n=337)
Median f/u 12.5 months

Dacarbazine (n=338)
Median f/u 9.5 months

Hazard ratio 0.70
(95% CI: 0.57–0.87) p<0.001 (post-hoc)

Time (months)

No. at risk
Dacarbazine 332 248 172 79 24 6 0
Vemurafenib 307 326 280 231 179 106 44 7 1

**Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations**

**Progression-Free Survival**

- Mono D: 5.8
- 150/1: 9.2
- 150/2: 9.4

Med follow up time 14 mo

**New England Journal of Medicine**
**coBRIM Study Design**

- Tumor cell
- 960 mg BID × 38 days (Days 1-28) +
  - Vemurafenib
  - Cetuximab
- 50 mg BID: × 21 days (Days 1-21)
- Disease progression, unacceptable toxicity, or withdrawal of consent

**Stratification**
- Geographic region
- Extent of disease (M1c vs other)

**Primary and point**
- FS, investigator-assessed

**Secondary endpoints**
- OS, objective response rate, duration of response, PFS, IRC-assessed, safety, pharmacokinetics, quality of life

**ITT Population**

<table>
<thead>
<tr>
<th>ITT Population</th>
<th>Cetuximab + Vemurafenib (n&gt;247)</th>
<th>Placebo + Vemurafenib (n&lt;248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n (%)</td>
<td>143 (57.8)</td>
<td>182 (72.4)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>12.25 (9.46-18.87)</td>
<td>7.20 (CI 5.50-7.49)</td>
</tr>
<tr>
<td>HR+ (95% CI)</td>
<td>0.58 (CI 0.40-0.79)</td>
<td>—</td>
</tr>
</tbody>
</table>

**Data cutoff**
- January 16, 2015

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**coBRIM Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Cetuximab + Vemurafenib (n&gt;247)</th>
<th>Placebo + Vemurafenib (n&lt;248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>60 (23-80)</td>
<td>55 (25-85)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 140 (57)</td>
<td>Female 104 (43)</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
  - Australia/New Zealand/Other Europe 40 (16) |
  - North America 164 (67) |
| ECOG, n (%)          |
  - PS 0 108 (78) |
  - PS 1 58 (14) |
  - PS 2 14 (5) |
| Previously treated brain metastases, n (%) | 1 (4) | 2 (8) |
| Stage at randomization, n (%) |
  - Unresectable stage IIIc 21 (9) |
  - Stage IV, M1a 40 (16) |
  - Stage IV, M1b 40 (16) |
  - Stage IV, M1c 146 (59) |
| Elevated LDH, n (%) | 112 (46) | 104 (43) |

**Median follow-up (range), months**
- 14.2 (3.5-24.8)

**Adaptive Resistance to T Cell Killing**

- Tumor cell
- Activated T cell
- Resting T cell
- CD28
- Lymph node
- Interferons
- Perforin

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**Notes**

- LDH, lactate dehydrogenase
- *The data cutoff was January 16, 2015. The median follow-up in the primary analysis was 7.3 months (range, 5.6-16.5). Lehrer et al. N Engl J Med. 2015;373:1862-1874.*
Long-term Efficacy of Pembrolizumab in a Pooled Analysis of 655 Patients With Advanced Melanoma Enrolled in KEYNOTE-001

Adil Daud,1 Antoni Ribas,2 Caroline Robert,3 F. Stephen Hodi,4 Jedd Wolchok,5 Anthony M. Joshua,6 Wen-Jen Hwu,7 Jeffrey S. Weber,8 Tara C. Gangadhar,9 Richard Joseph,10 Roxana Dronca,11 Amita Patnaik,12 Hassane Zarour,13 Richard Kefford,14,15 Jill A. Lindia,16 Xiaoyun Nicole Li,16 Scot Ebbinghaus,16 S. Peter Kang,16 Omid Hamid17

1University of California, San Francisco, CA; 2University of California, Los Angeles, CA; 3Institut Gustave-Roussy, Villejuif, France; 4Dana-Farber Cancer Institute, Boston, MA; 5Memorial Sloan-Kettering Cancer Center, New York, NY; 6Princess Margaret Hospital, Toronto, Ontario; 7MD Anderson Cancer Center, Houston, TX; 8H. Lee Moffitt Cancer Center, Tampa, FL; 9Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; 10Mayo Clinic, Jacksonville, FL; 11Mayo Clinic, Rochester, MN; 12South Texas Accelerated Research Therapeutics, San Antonio, TX; 13University of Pittsburgh, Pittsburgh, PA; 14Crown Princess Mary Cancer Centre, Westmead Hospital and Melanoma Institute Australia, Sydney, Australia; 15Macquarie University, Sydney, Australia; 16Merck & Co., Inc., Kenilworth, NJ; 17The Angeles Clinic and Research Institute, Los Angeles, CA

Pembrolizumab For Advanced Melanoma

• Anti–PD-1 humanized monoclonal antibody approved in various countries for the treatment of advanced melanoma
• Studied in 1572 patients with advanced melanoma
  • KEYNOTE-001: durable efficacy, manageable toxicity for IPI-naive and IPI-treated (N = 655)1-4
  • KEYNOTE-002: superior to chemotherapy, less toxicity after progression on IPI (N = 540)5
  • KEYNOTE-006: superior to IPI, less high-grade toxicity for IPI-naive (N = 834)6
• Approved dose: 2 mg/kg IV over 30 minutes every 3 weeks
  • 5 randomized comparisons: no significant difference between 2 and 10 mg/kg Q3W or Q2W2,3,5

KEYNOTE-001: Melanoma Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N = 655</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>M stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>61%</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>M1a</td>
<td>8%</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>M1b</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>M1c</td>
<td>78%</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td>No. of prior systemic therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>1</td>
<td>31%</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>2</td>
<td>27%</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>≥3</td>
<td>17%</td>
<td>17%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Type of previous therapy7

Ipilimumab: 52%
Chemo + ipilimumab: 33%
BRAF inhibitor: 17%
Other immunotherapy: 26%
Other therapy: 14%

Includes neoadjuvant therapies. Patients may have received ≥1 type of previous therapy.
Includes BRAF inhibitors. Excludes ipilimumab.
Analysis date: April 18, 2015

Characteristic | Total N = 655
Age, median (range), y | 61.0 (18-94)
Sex | 62%
ECOG PS | 0 68% 1 32%
BRAF status | Mutant 24% Wild type 75% Unknown 1%
History of brain metastases | 8%
LDH > ULN | 38%
Tumor size at baseline, median (range), mm | 102 (10-895)
Immune-Mediated AEs of Interest

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>n (%)</th>
<th>Any Grade</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>49 (7.5)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>15 (2.3)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis$^a$</td>
<td>18 (2.7)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Colitis$^b$</td>
<td>11 (1.7)</td>
<td>7 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis$^c$</td>
<td>4 (0.6)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Nephritis$^d$</td>
<td>3 (0.5)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Uveitis$^e$</td>
<td>6 (0.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Includes interstitial lung disease of grade 1-2.
$^b$Includes colitis microscopic and enterocolitis.
$^c$Includes autoimmune hepatitis.
$^d$Includes renal failure.
$^e$Includes iridocyclitis and iritis.

- Some reported skin rashes may have been immune-mediated
- Other immune-mediated events observed in >2 patients: thyroiditis (n = 6); hypophysitis, hypopituitarism, pruritus, and rash (n = 3 each); autoimmune thyroiditis, myositis, and rash generalized (n = 2 each)

Efficacy in Total Population (RECIST v1.1, Central Review)

- CR, % (95% CI): 8 (6-11)
- ORR, % (95% CI): 33 (30-37)

ORR in Subgroups of Total Population (RECIST 1.1, Central Review)

Efficacy in Total Population (RECIST v1.1, Central Review)

Survival in Total Population (RECIST 1.1, Central Review)

- Median (95% CI): 22.8 months (19.8-28.7)
- Rate at 24 months: 49%
Efficacy as First-Line Therapy
REcIST v1.1, Central Review

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 133)</th>
<th>B RAF V600 Wild Type (n = 109)</th>
<th>B RAF V600 Mutant (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response, % (95% CI)</strong></td>
<td>13.5 (8.2-20.5)</td>
<td>12.8 (7.2-20.6)</td>
<td>18.2 (5.2-40.3)</td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>45.1 (36.5-54.0)</td>
<td>45.0 (35.4-54.8)</td>
<td>50.0 (28.2-71.8)</td>
</tr>
<tr>
<td><strong>DCR, % (95% CI)</strong></td>
<td>60.9 (52.1-69.2)</td>
<td>60.6 (50.7-69.8)</td>
<td>63.6 (40.7-82.8)</td>
</tr>
</tbody>
</table>

*Excludes patients with ocular melanoma.
Analysis cut-off date: October 18, 2014.

PD-L1 Expression and Relationship With Response

<table>
<thead>
<tr>
<th>PD-L1 Expression</th>
<th>ORR, RECIST v1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>APS = 0</td>
</tr>
<tr>
<td>Positive</td>
<td>APS = 1-10%</td>
</tr>
<tr>
<td>Positive</td>
<td>APS = 10-33%</td>
</tr>
<tr>
<td>Positive</td>
<td>APS = 66-100%</td>
</tr>
</tbody>
</table>

*APS, Allred proportion score.
Analysis cut-off date: October 18, 2014.

KEYNOTE-006 (NCT01866319): International, *a* Randomized, Phase III Study

**Patients**
- Unresectable, stage III or IV melanoma
- 1 prior therapy, excluding anti-CTLA-4, PD-1, or PD-L1 agents
- Known B RAF status* 
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease

**Stratification factors:**
- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive vs negative)

*Prior and PD-1/PD-L1 targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

**Key Points:**
- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety

**Study Design:**
- 1:1:1 ratio
- Pembrolizumab 10 mg/kg IV Q2W
- pembrolizumab 10 mg/kg IV Q3W
- ipilimumab 3 mg/kg IV Q3W x 4 doses

*Excludes patients with ocular melanoma.
Analysis cut-off date: October 18, 2014.

**Outcomes in the First-Line population**

- **PFS**
  - Median (95% CI): 13.8 months (6.7-17.4)
  - Rate at 12 months: 52%

- **OS**
  - Median (95% CI): 31.1 months (24.4-NR)
  - Rate at 24 months: 60%
Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab Q2W n = 279</th>
<th>Pembrolizumab Q3W n = 277</th>
<th>Ipilimumab n = 278</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range), y</strong></td>
<td>61 (18-89)</td>
<td>63 (22-89)</td>
<td>62 (18-88)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>57.7%</td>
<td>62.8%</td>
<td>58.3%</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>70.3%</td>
<td>68.2%</td>
<td>67.6%</td>
</tr>
<tr>
<td>1</td>
<td>29.7%</td>
<td>31.8%</td>
<td>32.4%</td>
</tr>
<tr>
<td><strong>BRAF status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant</td>
<td>35.1%</td>
<td>35.0%</td>
<td>38.5%</td>
</tr>
<tr>
<td>Wild type</td>
<td>64.9%</td>
<td>64.9%</td>
<td>61.2%</td>
</tr>
<tr>
<td><strong>LDH level</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>80.2%</td>
<td>61.3%</td>
<td>64.0%</td>
</tr>
<tr>
<td>Elevated</td>
<td>19.8%</td>
<td>35.6%</td>
<td>36.0%</td>
</tr>
<tr>
<td><strong>M stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>2.2%</td>
<td>3.2%</td>
<td>5.8%</td>
</tr>
<tr>
<td>M1</td>
<td>2.2%</td>
<td>1.4%</td>
<td>1.8%</td>
</tr>
<tr>
<td>M1a</td>
<td>7.5%</td>
<td>12.3%</td>
<td>10.8%</td>
</tr>
<tr>
<td>M1b</td>
<td>22.9%</td>
<td>14.8%</td>
<td>18.7%</td>
</tr>
<tr>
<td>M1c</td>
<td>64.2%</td>
<td>68.2%</td>
<td>63.7%</td>
</tr>
</tbody>
</table>

PFS at the First Interim Analysis (IA1)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 6 mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab Q2W</td>
<td>5.5 (3.4-6.9)</td>
<td>47.3%</td>
<td>0.58 (0.46-0.72)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Pembrolizumab Q3W</td>
<td>4.1 (2.8-5.8)</td>
<td>46.4%</td>
<td>0.58 (0.47-0.72)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>2.8 (2.6-3.0)</td>
<td>26.5%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

OS at the Second Interim Analysis (IA2)

Best Percentage Change From Baseline in Target Lesions at IA1 (RECIST v1.1, Central Review)
**Primary Endpoint: Overall Survival**

Nivolumab (N=210) vs Dacarbazine (N=208) in patients with untreated advanced melanoma. Updated analysis presented at ASCO 2015.

- **HR 0.42 (99.79% CI, 0.25-0.73; P < 0.0001)**

**Follow-up since randomization: 5.2-16.7 months**

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**Nivolumab Improved Survival vs Dacarbazine in Patients with Untreated Advanced Melanoma**

- **1-yr OS 73%** for Nivolumab
- **1-yr OS 42%** for Dacarbazine

**Patients who died:**
- Nivolumab: 42 patients (20.5%)
- Dacarbazine: 50 patients (24.1%)

**Median OS**:
- Nivolumab: 11 months
- Dacarbazine: Not reached

**Secondary endpoints**:
- **Colitis**
- **Hepatitis**
- **Pneumonitis**
- **T1DM**
- **Uveitis**
- **Myositis**
- **Nephritis**

**Incidence not adjusted for duration of exposure.**

Analysis cut-off date: September 3, 2014.
**Secondary Endpoint: PFS**

Based on 5 August 2014 database lock

HR 0.43 (95% CI, 0.34–0.56; P < 0.0001)

**Patients without Progression (%)**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (mo)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>5.1 (3.5–10.8)</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>2.2 (1.4–7.6)</td>
<td></td>
</tr>
</tbody>
</table>

**Patients who Died**, **n/N**

<table>
<thead>
<tr>
<th></th>
<th>Median OS (mo)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab PD-L1+</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine PD-L1+</td>
<td>12.4 (9.2–NR)</td>
<td></td>
</tr>
<tr>
<td>Nivolumab PD-L1-</td>
<td>37/128</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine PD-L1-</td>
<td>64/126</td>
<td>10.2 (7.6–11.8)</td>
</tr>
</tbody>
</table>

**Patients at Risk**

- Nivolumab PD-L1+: 116 patients
- Nivolumab PD-L1-: 74 patients
- Dacarbazine PD-L1+: 29 patients
- Dacarbazine PD-L1-: 64 patients

**Patients Surviving (%)**

- Nivolumab PD-L1+: 100%
- Dacarbazine PD-L1+: 78%
- Nivolumab PD-L1-: 88%
- Dacarbazine PD-L1-: 52%

**CA209-067: Study Design**

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

**Treat until progression** or unacceptable toxicity

- NIVOD 3 mg/kg + IPI 3 mg/kg Q2W
- Dacar 3 mg/kg Q2W

**Randomize 1:1:1**

- Stratify by:
  - PD-L1 expression
  - BRAF status
  - AJCC M stage

**Verifed 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.**
**Study Endpoints: NIVO or NIVO + IPI vs. IPI**

**Co-primary endpoints:**
- Progression-free survival (PFS) and overall survival (OS) (intent-to-treat population)

**Secondary and other endpoints:**
- ORR by RECIST v1.1
- Predefined tumor PD-L1 expression level as a predictive biomarker of efficacy
- Safety profile (in patients who received ≥1 dose of study drug)

**Current analysis:**
- PFS with follow-up of at least 9 months in all patients (83% power to detect an HR of 0.71)
  - Study was not powered for a comparison between NIVO + IPI and NIVO alone
- Database lock: February 17, 2015
- Study remains blinded for OS as per study design until planned number of events has been reached (minimum 22 months of follow-up)

### PFS (Intent-to-Treat)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS, months (95% CI)</th>
<th>HR (99.5% CI) vs. IPI</th>
<th>HR (95% CI) vs. NIVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>11.5 (8.9–16.7)</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.74 (0.60–0.92)**</td>
</tr>
<tr>
<td>NIVO</td>
<td>6.9 (4.3–9.5)</td>
<td>0.57 (0.43–0.76)*</td>
<td>--</td>
</tr>
<tr>
<td>IPI</td>
<td>2.9</td>
<td>2.0</td>
<td>--</td>
</tr>
</tbody>
</table>

*Stratified log-rank P < 0.00001 vs. IPI
**Exploratory endpoint

### Tumor Burden Change From Baseline

- **NIVO + IPI:** Median change: -51.9%
  - Baseline reduction from baseline in target lesions (%)
  - Confirmed responder
  - 30% reduction in tumor burden by RECIST v1.1

- **NIVO:** Median change: -34.5%

### PFS by PD-L1 Expression Level (5%)

- **PD-L1 ≥5%**
  - No. at Risk
  - Months
  - Proportion alive and progression-free
  - mPFS HR

- **PD-L1 <5%**
  - No. at Risk
  - Months
  - Proportion alive and progression-free
  - mPFS HR

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

Advances in Immunotherapy

Advances in BRAF and BRAF mutant melanoma

Challenges remain in Uveal and Mucosal Melanoma

Early Detection and Sun Protection remain important

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