Medical Treatment for Melanoma

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Disclosures

None
Overview

• Current Therapy for Metastatic Disease
  – Immunotherapy
  – Targeted Therapy

• Current Status of Adjuvant Therapy
Transforming the Landscape
Hit a Target

Immunotherapy
Target host

Targeted Therapy
Target tumor
Current Therapeutic Options for Patients with Metastatic Melanoma

• For BRAF-WT Patients
  – Immunotherapy
    • Monotherapy or combination?

• For BRAF+ Patients
  – Immunotherapy or targeted therapy
    • What is the correct sequence?
Current Therapeutic Options for Patients with Metastatic Melanoma

• For BRAF-WT Patients
  – Immunotherapy
    • Monotherapy or combination?

• For BRAF+ Patients
  – Immunotherapy or targeted therapy
    • What is the correct sequence?
Targeted Immunotherapy

= Checkpoint Inhibitors
What is a “Check-Point”? 
T-Cell Activity Is Regulated By Immune Checkpoints to Limit Autoimmunity

Activated T cell

Immune checkpoints, such as CTLA-4, PD-1, LAG-3, and TIM-3 function at different phases in the immune response to regulate the duration and level of the T-cell response.

CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1; LAG-3 = lymphocyte activation gene 3; TIM-3 = T-cell immunoglobulin and mucin protein 3.

What is a “Check-Point” Inhibitor?
Immune System

Cytokines

Antigens

Regulatory molecules (CTLA-4, PD-1)

Immunotherapy
Check-Point Inhibitors Approved for Melanoma

- Anti CTLA4 (ipilimumab)
- Anti PD-1 (pembrolizumab, nivolumab)
- Combination anti CTLA-4 and anti-PD1 (ipilimumab and nivolumab)
Clinical Results with Ipilimumab (2nd and 1st line)
Ipilimumab vs vaccine and Ipi + DTIC vs DTIC

HR: 0.66 and 0.68
Pre-treated pts
Ipi 3 mg/kg +/- gp100

HR: 0.72
First line
Ipi 10 mg/kg + DTIC


Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma

Ipilimumab became the standard of care in 2011

But can we do better?
Keynote-006 Front-line Pembrolizumab vs Ipilimumab

Patients
- Unresectable, stage III or IV melanoma
- ≤1 prior therapy, excluding anti–CTLA-4, PD-1, or PD-L1 agents
- Known **BRAF** 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)

- **Pembrolizumab 10 mg/kg IV Q2W**
- **Pembrolizumab 10 mg/kg IV Q3W**
- **Ipilimumab 3 mg/kg IV Q3W x 4 doses**

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

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*a* Patients enrolled from 83 sites in 16 countries.

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

*c* Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.
# Tumor Response (irRC, investigator)

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (N = 556)</th>
<th>Ipilimumab (N = 278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>42 (38-46)</td>
<td>16 (12-21)</td>
</tr>
<tr>
<td>Best overall response, % (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>13 (11-16)</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td>PR</td>
<td>29 (25-33)</td>
<td>14 (10-18)</td>
</tr>
<tr>
<td>SD</td>
<td>21 (18-25)</td>
<td>25 (20-31)</td>
</tr>
<tr>
<td>PD</td>
<td>29 (26-33)</td>
<td>39 (33-45)</td>
</tr>
</tbody>
</table>
Kaplan-Meier Estimates of Survival (Median Follow-Up, 33.9 mo)

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>Median, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>278</td>
<td>0.70 (0.58-0.86)</td>
<td>32.3 (24.5-NR)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>155</td>
<td>-</td>
<td>15.9 (13.3-22)</td>
</tr>
</tbody>
</table>

PFS per irRC by Investigator

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>Median, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>369</td>
<td>0.56 (0.47-0.67)</td>
<td>8.3 (6.5-11.2)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>204</td>
<td>-</td>
<td>3.3 (2.9-4.1)</td>
</tr>
</tbody>
</table>

PFS (irRC, investigator) From Last Pembrolizumab Dose to PD or Death in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 104)

- 102 (98%) patients were alive after a median of 9.7 months after completing pembrolizumab treatment
PFS (irRC, investigator) From Last Pembrolizumab Dose to PD or Death in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 104) (cont)

<table>
<thead>
<tr>
<th>Best Response</th>
<th>n</th>
<th>Estimated PFS, % (95% CI)</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>24</td>
<td>95 (69-99)</td>
<td>NR</td>
</tr>
<tr>
<td>PR</td>
<td>68</td>
<td>91 (74-97)</td>
<td>NR</td>
</tr>
<tr>
<td>SD</td>
<td>12</td>
<td>83 (48-96)</td>
<td>NR</td>
</tr>
</tbody>
</table>
Treatment Exposure and Response Duration in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 104)

- CR
- PR
- PD
- Death
- Patient with CR or PR
- Patient with SD
- Patient with ongoing CR or PR
Anti PD-1 is better than ipilimumab frontline and responses are durable even after stopping treatment.

But what about combining CTLA-4 and PD-1?
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:
- PD-L1 expression*
- BRAF 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

Treat until progression** or unacceptable toxicity

N=315

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

*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.
Updated 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>58.9 (53.3–64.4)</td>
<td>44.6 (39.1–50.3)</td>
<td>19.0 (14.9–23.8)</td>
</tr>
<tr>
<td><strong>Best overall response — %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>17.2</td>
<td>14.9</td>
<td>4.4</td>
</tr>
<tr>
<td>Partial response</td>
<td>41.7</td>
<td>29.7</td>
<td>14.6</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11.5</td>
<td>9.8</td>
<td>21.3</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>23.6</td>
<td>38.6</td>
<td>51.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.1</td>
<td>7.0</td>
<td>8.6</td>
</tr>
<tr>
<td><strong>Median duration of response, months (95% CI)</strong></td>
<td>NR (NR–NR)</td>
<td>31.1 (31.1–NR)</td>
<td>18.2 (8.3–NR)</td>
</tr>
</tbody>
</table>

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

- At the 18-month DBL, the CR rate for NIVO+IPI, NIVO and IPI was 12.1%, 9.8% and 2.2%, respectively.

Database lock: Sept 13, 2016, minimum f/u of 28 months
Updated Progression-Free Survival

### Median PFS, mo (95% CI)
- **NIVO+IPI (N=314)**: 11.7 (8.9–21.9)
- **NIVO (N=316)**: 6.9 (4.3–9.5)
- **IPI (N=315)**: 2.9 (2.8–3.2)

### HR (95% CI) vs. IPI
- **NIVO+IPI (N=314)**: 0.42 (0.34–0.51)
- **NIVO (N=316)**: 0.54 (0.45–0.66)
- **IPI (N=315)**: --

### HR (95% CI) vs. NIVO
- **NIVO+IPI (N=314)**: 0.76 (0.62–0.94)
- **NIVO (N=316)**: --
- **IPI (N=315)**: --

#### Patients at risk:
- **NIVO+IPI**: 314 → 218 → 176 → 156 → 137 → 132 → 125 → 118 → 110 → 104 → 71 → 16 → 0
- **NIVO**: 316 → 178 → 151 → 132 → 120 → 112 → 107 → 103 → 97 → 88 → 62 → 16 → 0
- **IPI**: 315 → 136 → 77 → 58 → 46 → 43 → 35 → 33 → 30 → 27 → 16 → 5 → 0

**Database lock: Sept 13, 2016, minimum f/u of 28 months**
Updated Survival Data in CheckMate-067 Trial of IPI vs. NIVO vs. IPI/NIVO

<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>Median OS, months</td>
<td>NR</td>
<td>NR (29.1-NR)</td>
<td>20 (17.1-24.6)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (99.5% CI) vs. IPI</td>
<td>0.55 (0.42–0.72)*</td>
<td>0.63 (0.48–0.81)*</td>
<td>-</td>
</tr>
<tr>
<td>HR (99.5% CI) vs. NIVO</td>
<td>0.88 (0.69-1.12)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\*P<0.0001

Decision Point....

Immunotherapy

- PD-1 alone
- PD-1/CTLA-4 Combination
Checkmate 067: Safety Summary

- With an additional 19 months of follow-up, safety was consistent with the initial report

<table>
<thead>
<tr>
<th>Patients reporting event, %</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>Treatment-related adverse event (AE)</td>
<td>95.8</td>
<td>58.5</td>
<td>86.3</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>39.6</td>
<td>31.0</td>
<td>11.5</td>
</tr>
<tr>
<td>Treatment-related death, n (%)</td>
<td>2 (0.6)a</td>
<td>1 (0.3)b</td>
<td>1 (0.3)b</td>
</tr>
</tbody>
</table>

- Most select AEs were managed and resolved within 3-4 weeks (85–100% across organ categories)
- ORR was 70.7% for pts who discontinued NIVO+IPI due to AEs, with median OS not reached

aCardiomyopathy (NIVO+IPI, n=1); Liver necrosis (NIVO+IPI, n=1). Both deaths occurred >100 days after the last treatment.
bNeutropenia (NIVO, n=1); colon perforation (IPI, n=1).

Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs

Toxicity Earlier
Longer Time to Resolution

Circles represent medians; bars signify ranges

Larkin J et al ECC 2015
Incidence of Immune-Mediated AEs

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Mean Exposure</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous1</td>
<td>11.4 mo</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>12.7 mo</td>
<td></td>
</tr>
</tbody>
</table>

Based on a list determined by the sponsor and regardless of attribution by the investigator.

Can a biomarker help us decide?
Keynote 001 Pembrolizumab
PD-L1 Expression and Response

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

PD-L1 Negative
0% Staining
APS = 0

PD-L1 Positive
1-10% Staining
APS = 2

PD-L1 Positive
10-33% Staining
APS = 3

PD-L1 Positive
66-100% Staining
APS = 5

ORR, RECIST v1.1

APS 0
n = 28

APS 1
n = 24

APS 2
n = 72

APS 3
n = 54

APS 4
n = 32

APS 5
n = 34

Daud A et al, ASCO 2015
OS by Tumor PDL-1 Expression at a 1% Cutoff

**PD-L1 Expression Level <1%**

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR (26.5–NR)</td>
<td>23.5 (13.0–13.7)</td>
<td>18.6 (13.7–23.2)</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO</td>
<td>0.74 (0.52–1.06)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**PD-L1 Expression Level ≥1%**

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR</td>
<td>NR</td>
<td>22.1 (17.1–29.7)</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO</td>
<td>1.03 (0.72–1.48)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

• ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

• ORR of 65.2% for NIVO+IPI and 55.0% for NIVO
## PFS and OS Subgroup Analyses (All Randomized Patients)

Descriptive comparison between NIVO+IPI and NIVO

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>Unstratified Hazard Ratio</th>
<th>Unstratified Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIVO+IPI</td>
<td>NIVO</td>
<td>PFS</td>
</tr>
<tr>
<td>Overall</td>
<td>314</td>
<td>316</td>
<td>0.77</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>185</td>
<td>198</td>
<td>0.74</td>
</tr>
<tr>
<td>≥65 years</td>
<td>129</td>
<td>118</td>
<td>0.82</td>
</tr>
<tr>
<td>BRAF Mutant</td>
<td>102</td>
<td>98</td>
<td>0.60</td>
</tr>
<tr>
<td>BRAF Wild-type</td>
<td>212</td>
<td>218</td>
<td>0.86</td>
</tr>
<tr>
<td>ECOG PS = 0</td>
<td>230</td>
<td>237</td>
<td>0.79</td>
</tr>
<tr>
<td>ECOG PS = 1</td>
<td>83</td>
<td>78</td>
<td>0.72</td>
</tr>
<tr>
<td>M0/M1a/M1b</td>
<td>129</td>
<td>132</td>
<td>0.67</td>
</tr>
<tr>
<td>M1c</td>
<td>185</td>
<td>184</td>
<td>0.83</td>
</tr>
<tr>
<td>LDH ≤ ULN</td>
<td>199</td>
<td>197</td>
<td>0.72</td>
</tr>
<tr>
<td>LDH &gt; ULN</td>
<td>114</td>
<td>112</td>
<td>0.79</td>
</tr>
<tr>
<td>LDH &gt; 2 x ULN</td>
<td>37</td>
<td>37</td>
<td>0.70</td>
</tr>
<tr>
<td>PD-L1 ≥5%</td>
<td>68</td>
<td>80</td>
<td>0.87</td>
</tr>
<tr>
<td>PD-L1 &lt;5%</td>
<td>210</td>
<td>208</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Current Therapeutic Options for Patients with Metastatic Melanoma

• For BRAF-WT Patients
  – Immunotherapy
    • Monotherapy or combination?

• For BRAF+ Patients
  – Immunotherapy or targeted therapy
    • What is the correct sequence?
Melanoma is not one disease

B-RAF: 50%
c-kit: 5-10%
c-kit: 10-20%
c-kit: 15-30%
MAPK Pathway

Growth Factors

RAS

BRAF

MEK

ERK

Cell proliferation and survival

Cell proliferation and survival
BRAF Mutation

BRAF mutation is present in ~50% of melanomas

Increased cell proliferation and survival
MAPK Pathway Targeted Therapy

**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 III studies

**Dabrafenib + trametinib (D + T)**
- PFS HR, 0.67 vs dabrafenib\(^4\)
- OS HR, 0.71 vs dabrafenib\(^4\)
- PFS HR, 0.56 vs vemurafenib\(^5\)
- OS HR, 0.69 vs vemurafenib\(^5\)

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

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

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Decision Point....

BRAF mutation test

BRAF<sup>V600</sup> mutation negative
- Immunotherapy

BRAF<sup>V600</sup> mutation positive
- Immunotherapy
  - Or
  - MAP-K Targeted Therapy
Antitumoral response: Targeted therapies vs. Immunotherapies (CTLA-4 antibodies)
Part C: Study Design (phase 2)

Key eligibility criteria
- ≥ 18 years of age
- Unresectable stage IIIIC or IV BRAF V600E/K-mutant melanoma
- ECOG PS 0 or 1
- No prior treatment with BRAF or MEK inhibitor
- ≤ 1 previous line of chemotherapy
- Brain metastases allowed if treated and stable for ≥ 3 months

Randomization 1:1:1

- Dabrafenib 150 mg BID + trametinib 2 mg QD
  - n = 54
- Dabrafenib 150 mg BID + trametinib 1 mg QD
  - n = 54
- Dabrafenib 150 mg BID
  - n = 54

Primary endpoints are ORR, DOR, PFS, and safety
Secondary endpoints are pharmacokinetics and OS

Crossover allowed upon progression
- Dabrafenib 150 mg BID + trametinib 2 mg QD
  - n = 45

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Presented by: Jeffrey Weber
OS (Intent-to-Treat)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+T 150/2</td>
<td>25.0 (17.5-36.5)</td>
</tr>
<tr>
<td>D+T 150/1</td>
<td>22.5 (14.2-42.3)</td>
</tr>
<tr>
<td>D Monotherapy</td>
<td>20.2 (14.5-27.1)</td>
</tr>
</tbody>
</table>

Overall Survival, %

Patients at risk, n

<table>
<thead>
<tr>
<th>Time From Randomization, months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>54</th>
<th>60</th>
<th>66</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>52</td>
<td>43</td>
<td>33</td>
<td>27</td>
<td>23</td>
<td>20</td>
<td>18</td>
<td>15</td>
<td>14</td>
<td>14</td>
<td>4</td>
<td>0</td>
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</tr>
<tr>
<td>54</td>
<td>48</td>
<td>38</td>
<td>25</td>
<td>23</td>
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<tr>
<td>54</td>
<td>50</td>
<td>38</td>
<td>30</td>
<td>24</td>
<td>20</td>
<td>16</td>
<td>14</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>2</td>
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</tr>
</tbody>
</table>
Pembro Keynote 001: 4 Year OS

Robert, EADO, Jun 2017

Overall Survival

All Patients

<table>
<thead>
<tr>
<th>Pts, N</th>
<th>Events, n</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>655</td>
<td>388</td>
<td>23.8 mo (20.2-30.4 mo)</td>
</tr>
</tbody>
</table>

Treatment Naive

<table>
<thead>
<tr>
<th>Pts, N</th>
<th>Events, n</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>152</td>
<td>76</td>
<td>41.2 mo (27.2 mo-NR)</td>
</tr>
</tbody>
</table>

Excludes patients with ocular melanoma.
Analysis cutoff date: September 1, 2016.
Phase III KEYNOTE-006:
PFS in Prespecified Subgroups

### Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup Category</th>
<th>Pembrolizumab Q2W vs ipilimumab</th>
<th>Pembrolizumab Q3W vs ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>557</td>
<td>555</td>
</tr>
<tr>
<td>Male</td>
<td>323</td>
<td>336</td>
</tr>
<tr>
<td>Female</td>
<td>234</td>
<td>219</td>
</tr>
<tr>
<td>Age &lt;65 y</td>
<td>319</td>
<td>318</td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>238</td>
<td>237</td>
</tr>
<tr>
<td>White race</td>
<td>545</td>
<td>543</td>
</tr>
<tr>
<td>US</td>
<td>114</td>
<td>111</td>
</tr>
<tr>
<td>Rest of world</td>
<td>443</td>
<td>444</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>384</td>
<td>377</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>173</td>
<td>178</td>
</tr>
<tr>
<td>First-line therapy</td>
<td>364</td>
<td>366</td>
</tr>
<tr>
<td>Second-line therapy</td>
<td>193</td>
<td>188</td>
</tr>
<tr>
<td>PD-L1 positive</td>
<td>450</td>
<td>446</td>
</tr>
<tr>
<td>PD-L1 negative</td>
<td>96</td>
<td>101</td>
</tr>
<tr>
<td>BRAF wild type</td>
<td>347</td>
<td>348</td>
</tr>
<tr>
<td>BRAF mutant, prior anti-BRAF</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>BRAF mutant, no prior anti-BRAF</td>
<td>110</td>
<td>108</td>
</tr>
<tr>
<td>No prior immunotherapy</td>
<td>537</td>
<td>536</td>
</tr>
</tbody>
</table>

Analysis cut-off date: September 3, 2014.
KEYNOTE-001: Phase I
RECIST Response (v1.1)

Total population n=581
ORR 33%
CR 8%

Median Change:
-36%

Treatment naïve n=152
ORR 45%
CR 14%

Median Change:
-54%

Analysis cut-off date: October 18, 2014; Median follow up 21 mo

Daud A et al ASCO 2015
# BRAF Inhibitors

<table>
<thead>
<tr>
<th>Phase</th>
<th>Vemurafenib(^1)</th>
<th>Dabrafenib(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>PFS</td>
</tr>
<tr>
<td>Phase</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>RR</td>
<td>56%</td>
<td>57%</td>
</tr>
<tr>
<td>PFS</td>
<td>6.7</td>
<td>6.9</td>
</tr>
<tr>
<td>OS</td>
<td>13.8</td>
<td>15.9</td>
</tr>
</tbody>
</table>

D+T: Long Term FU
LDH < ULN and < 3 metastatic sites (ITT)

**Progression-Free Survival**

- Patients at risk, n: 19 16 12 10 9 8 8 5 3 3 3 3 0
- Time From Randomization, months: 0 6 12 18 24 30 36 42 48 54 60 66
- Progression-Free Survival, %: 100 82 75 68 61 54 47 40 33 26 19 12 5

**Overall Survival**

- Patients at risk, n: 19 19 18 15 15 14 14 13 10 9 9 3 0
- Time From Randomization, months: 0 6 12 18 24 30 36 42 48 54 60 66 72
- Overall Survival, %: 100 86 74 62 50 38 26 14 5 0

EA6134

Contemplating the Options

Anti-PD1 therapy vs. BRAF-targeted therapy

ECOG PS
- 0
- 1

Serum LDH

RANDOMIZE

Arm A:
- Ipilimumab 3mg/kg IV q 3wks x 4
- Nivolumab 1mg/kg IV q 3wks x 4
  Followed by Nivolumab 3 mg/kg IV q2 wks x 42

Dabrafenib 150mg po BID
Trametinib 2 mg daily

Arm B:
- Dabrafenib 150mg po BID
- Nivolumab 1 mg/kg IV q3 wks x 4
  Followed by Nivolumab 3 mg/kg IV q3 wks x 42

Ipilimumab 3mg/kg IV q 3wks x 4
Nivolumab 1 mg/kg IV q3 wks x 4
Will sequence not matter in the future??
• BRAF inhibitor alone or BRAF + MEK inhibitors → rapid and clinically significant responses
• Immunotherapy → less frequent objective responses, but clinically significant durability
• Combining targeted therapy with immunotherapy
  – Can harness and perpetuate the enhanced anti-tumor response following targeted inhibition
  – May lead to durable response and prolonged survival

Melanoma survival curves depending on the type of therapy

Figure modified from Ribas A et al. Clin Cancer Res 2012 and Hamid O et al. SMR 2015.
Targeted-Immuno Triplets: BRAF + MEK + PD1/L1

Multiple Triplet Combinations Launching Into Phase III:

- Dabrafenib + Trametinib + Pembrolizumab
- Dabrafenib + Trametinib + PDR-001
- Vemurafenib + Cobimetinib + Atezolizumab
Overview

• Current Therapy for Metastatic Disease
  – Immunotherapy
  – Targeted Therapy

• Current Status of Adjuvant Therapy
Distribution of Melanoma Burden by Stage

Unresectable Stage III, IV

Intermediate and high-risk resectable Stage IIB, IIC, III

Low risk resectable MIS Stage IA, IB, IIA

The burden of high risk disease dwarfs that of advanced melanoma and is an important clinical problem
Adjuvant Therapy

- The Old
  - Interferon
- The New
  - Ipilimumab
- The Future
## Adjuvant IFN-α Regimens

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 MIU</td>
<td>3 x weekly</td>
<td>18 – 24 months</td>
</tr>
<tr>
<td><strong>Intermediate Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>10 MIU</td>
<td>5 x weekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>10 MIU/m²</td>
<td>3 x weekly</td>
<td>12 -24 months</td>
</tr>
<tr>
<td></td>
<td>5 MIU</td>
<td>3 x weekly</td>
<td>24 months</td>
</tr>
<tr>
<td><strong>High Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>20 MIU/m²</td>
<td>5 x weekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>10 MIU/m²</td>
<td>3 x weekly</td>
<td>11 months</td>
</tr>
<tr>
<td><strong>Short Course</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction X 1</td>
<td>20 MIU/m²</td>
<td>5 x weekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Intermittent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction X 3</td>
<td>20 MIU/m²</td>
<td>20 MIU/m²</td>
<td>5 x weekly for 4 weeks Q 4 months</td>
</tr>
</tbody>
</table>
E1684: Updated Efficacy
(ITT at 12.6 yr Median Follow-up)

Relapse-Free Survival
Log-rank test: $P_2 = .02; P_1 = .01$

Overall Survival
Log-rank test: $P_2 = .18; P_1 = .09$.

<table>
<thead>
<tr>
<th>Treatment groups (N = 286)</th>
<th>Total</th>
<th>Dead or relapsed</th>
<th>Alive or relapsed-free</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>140</td>
<td>106</td>
<td>34</td>
<td>1.0</td>
</tr>
<tr>
<td>High-dose IFN</td>
<td>146</td>
<td>95</td>
<td>51</td>
<td>1.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment groups (N = 286)</th>
<th>Total</th>
<th>Dead</th>
<th>Alive</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>140</td>
<td>95</td>
<td>45</td>
<td>2.7</td>
</tr>
<tr>
<td>High-dose IFN</td>
<td>146</td>
<td>93</td>
<td>53</td>
<td>3.8</td>
</tr>
</tbody>
</table>
Tweaking Interferon

- Shorten the duration of HDI – high dose IV only
- Use pegylated IFN – once weekly dosing, lower dose with comparable AUC
Study design: ECOG 1697

Patients with intermediate- and high-risk melanoma

Defined as T3:
- Breslow thickness >1.5 mm (AJCC 6th ed)
- >2.0 mm (AJCC 7th ed)
- or
- Any thickness with microscopically positive nodal disease (N1a–N2a)

Postoperative adjuvant IFN alfa-2b
- 20 MU/m²/day
- for 5 days/week
- x 4 weeks

Observation

Agarwala SS et al. J Clin Oncol March 2017
E1697 Induction Only HD IFN vs Observation

Agarwala SS et al: Journal of Clinical Oncology 35, no. 8 (March 2017) 885-892
EORTC 18991 (PEG-IFN): Design

Patients (n=1,256):
Resected TxN1-2M0 melanoma, within 7 weeks of lymphadenectomy

Stratified by:
- Microscopic (N1) vs. palpable (N2)
- 1 vs. 2-4 vs. 5+ nodes
- Breslow
- Ulceration
- Gender
- Site

Primary Endpoints:
- Relapse-free survival (RFS)
- Distant metastasis-free survival (DMFS)

Randomization

Observation

Peg-IFN alfa-2b
- Induction (8 weeks) 6 µg/kg/week
- Maintenance (5 years or distant metastasis) 3 µg/kg/week
- Dose reduction to 3, 2, 1 to maintain performance status
EORTC 18991: RFS

<table>
<thead>
<tr>
<th>Patients Alive Without Relapse (%)</th>
<th>Observation</th>
<th>Peg-IFN-α2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-yr rate (SE)</td>
<td>38.9% (2.2)</td>
<td>45.6% (2.2)</td>
</tr>
<tr>
<td>Median (mos)</td>
<td>25.6</td>
<td>34.8</td>
</tr>
</tbody>
</table>

$p = .01$  HR = 0.82 (95% CI 0.71, 0.96)

Adjuvant Therapy

• The Old
  – Interferon
• The New
  – Ipilimumab
• The Future
Ipilimumab in Melanoma

• Standard Dose
  – 3mg/kg
  – Approved in metastatic melanoma

• High Dose
  – 10mg/kg
  – Approved in adjuvant therapy of melanoma
**Ipilimumab (HD) vs Placebo**

**EORTC 18071/CA184-029: Study Design**

**INDUCTION**
- Ipilimumab 10 mg/kg Q3W X4
- Placebo Q3W X4

**MAINTENANCE**
- Ipilimumab 10 mg/kg Q12W up to 3 years
- Placebo Q12W up to 3 years

**Stratification factors:**
- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

Treatment up to a maximum 3 years, or until disease progression, intolerable toxicity, or withdrawal

Primary Endpoint: Recurrence-free Survival (IRC)

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Placebo</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.

EORTC 18071: Overall Survival

Patients alive (%)

<table>
<thead>
<tr>
<th></th>
<th>Ipiplimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths/patients</td>
<td>162 / 475</td>
<td>214 / 476</td>
</tr>
<tr>
<td>Hazard ratio (95.1% CI)*</td>
<td>0.72 (0.58 - 0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Log-rank P value*</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Stratified by stage at randomization

*Stratified by stage at randomization

Eggermont AMM et al NEJM 2016
## Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab (n = 471)</th>
<th>Placebo (n = 474)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any AE, %</td>
<td>98.7</td>
<td>54.1</td>
</tr>
<tr>
<td>Treatment-related AE, %</td>
<td>94.1</td>
<td>45.4</td>
</tr>
<tr>
<td>Treatment-related AE discontinuation, %</td>
<td>48.0</td>
<td>32.9</td>
</tr>
<tr>
<td>Any immune-related AE, %</td>
<td>90.4</td>
<td>41.6</td>
</tr>
</tbody>
</table>

- No new deaths due to drug-related AEs compared with the primary analysis
  - 5 patients (1.1%) in the ipilimumab group
    - 3 patients with colitis (2 with gastrointestinal perforations)
    - 1 patient with myocarditis
    - 1 patient had multiorgan failure with Guillain-Barré syndrome
  - No deaths related to study drug in the placebo group
Patients with resectable stage IIIB or IIIC or IV (M1a or M1b)

N=1500 +

Primary Endpoint: RFS, OS
Secondary Endpoints: Safety, Quality of life, immunologic correlates of RFS, OS
Completed accrual: 8/2014 - Results anticipated: 2018

Study Chair: A Tarhini
RFS: Ipi10 vs. Ipi3
(Concurrently randomized patients)

HR = 1.0, 95%
CI (0.81, 1.24)

---

Presented by: Ahmad Tarhini, MD, PhD
## Safety Summary

(Based on all toxicity data as of 3/2/17)

<table>
<thead>
<tr>
<th></th>
<th>Ipi3 (n = 516)</th>
<th>Ipi10 (n = 503)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any AE, %</td>
<td>98.4</td>
<td>53.3</td>
</tr>
<tr>
<td>Treatment-related AE, %</td>
<td>96.0</td>
<td>36.6</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation, %</td>
<td>34.9</td>
<td>25.0</td>
</tr>
<tr>
<td>Any immune-related AE, %</td>
<td>73.6</td>
<td>18.8</td>
</tr>
</tbody>
</table>
## Treatment Related Deaths

<table>
<thead>
<tr>
<th>Ipi3 (2 patients/516; 0.4%)</th>
<th>Ipi10 (8 patients/503; 1.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colitis / Bowel perforation</strong></td>
<td><strong>Colitis</strong></td>
</tr>
<tr>
<td><strong>Colitis / Death NOS</strong></td>
<td><strong>Colitis / Colonic perforation</strong></td>
</tr>
<tr>
<td>(Colitis requiring steroids &amp; infliximab. C-diff infection. D/C in stable condition. Withdrew consent. Death)</td>
<td></td>
</tr>
<tr>
<td><strong>Colitis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Colitis / Ventricular tachycardia</strong></td>
<td><strong>Colitis / Nervous system disorder</strong></td>
</tr>
<tr>
<td>(Gr4 Colitis, later rehab, DVT, pneumonia, VT)</td>
<td>(GI toxicity with subsequent neurologic decline; 81 y.o.)</td>
</tr>
<tr>
<td><strong>Pneumonitis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Thromboembolic event / Hypopituitarism</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac arrest</strong></td>
<td><strong>(Syncope, sepsis, sudden death)</strong></td>
</tr>
</tbody>
</table>

---

Presented by: Ahmad Tarhini, MD, PhD

ECOG-ACRIN cancer research group

Reshaping the future of patient care
Adjuvant Therapy

- The Old
  - Interferon
- The New
  - Ipilimumab
- The Future
The Future

• Anti PD-1 antibodies are better than anti CTLA-4 in metastatic melanoma
• Makes sense to test them in adjuvant therapy

• What about BRAF+ patients?
Patients with high-risk, completely resected stage IIIB/IIIC or stage IV melanoma

Enrollment period: March 30, 2015 to November 30, 2015

Stratified by:
1) Disease stage: IIIB/C vs IV M1a-M1b vs IV M1c
2) PD-L1 status at a 5% cutoff in tumor cells

Follow-up
Maximum treatment duration of 1 year

NIVO 3 mg/kg IV Q2W and IPI placebo IV Q3W for 4 doses then Q12W from week 24

IPI 10 mg/kg IV Q3W for 4 doses then Q12W from week 24 and NIVO placebo IV Q2W

1:1
n = 453
n = 453
Primary Endpoint: RFS

<table>
<thead>
<tr>
<th>Months</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>20</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>30</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>40</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>50</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>60</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>70</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>80</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>90</td>
<td>44</td>
<td>46</td>
</tr>
</tbody>
</table>

Number of patients at risk
- NIVO 453
- IPI 453

<table>
<thead>
<tr>
<th>Events/patients</th>
<th>NIVO 154/453</th>
<th>IPI 206/453</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>NR (16.6, NR)</td>
</tr>
<tr>
<td>HR (97.5% CI)</td>
<td>0.65 (0.51, 0.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
Safety Summary

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>NIVO (n = 452)</th>
<th>IPI (n = 453)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>438 (97)</td>
<td>446 (98)</td>
</tr>
<tr>
<td></td>
<td>115 (25)</td>
<td>250 (55)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>385 (85)</td>
<td>434 (96)</td>
</tr>
<tr>
<td></td>
<td>65 (14)</td>
<td>208 (46)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation</td>
<td>44 (10)</td>
<td>193 (43)</td>
</tr>
<tr>
<td></td>
<td>21 (5)</td>
<td>140 (31)</td>
</tr>
<tr>
<td>Treatment-related AE leading to</td>
<td>35 (8)</td>
<td>189 (42)</td>
</tr>
<tr>
<td>discontinuation</td>
<td>16 (4)</td>
<td>136 (30)</td>
</tr>
</tbody>
</table>

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose
EORTC 1325/ KEYNOTE 054

**Stratification factors:**
- Stage
- Region

- Surgery if clinically indicated and tumor material obtained from surgery or biopsy.
- Recurrence > 6 months after completion of 1 year pembrolizumab treatment
- After recurrence, patients assigned to placebo arm will be offered to crossover to pembrolizumab
Adjuvant Targeted Therapy
**COMBI-AD: STUDY DESIGN**

**Key eligibility criteria**
- Completely resected, high-risk stage IIA (lymph node metastasis > 1 mm), IIIB, or IIIC cutaneous melanoma
- *BRAF* V600E/K mutation
- Surgically free of disease ≤ 12 weeks before randomization
- ECOG performance status 0 or 1
- No prior radiotherapy or systemic therapy

**Stratification**
- *BRAF* mutation status (V600E, V600K)
- Disease stage (IIIA, IIIB, IIIC)

**Treatment: 12 months**
- Dabrafenib 150 mg BID + trametinib 2 mg QD (n = 438)
- 2 matched placebos (n = 432)

**Follow-up** until end of study

**Primary endpoint: RFS**
- Secondary endpoints: OS, DMFS, FFR, safety

BID, twice daily; DMFS, distant metastasis–free survival; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival.  

* Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent;  

* Patients were followed for disease recurrence until the first recurrence and thereafter for survival;  

* The study will be considered complete and final OS analysis will occur when ≥ 70% of randomized patients have died or are lost to follow-up;  

* New primary melanoma considered as an event.
RELAPSE-FREE SURVIVAL (PRIMARY ENDPOINT)

No. at Risk
Dabrafenib plus trametinib 438 413 405 392 382 373 355 336 325 299 282 276 263 257 233 202 194 147 116 110 66 52 42 19 7 2 0
Placebo 432 387 322 280 263 243 219 203 198 185 178 175 168 166 158 141 138 106 87 86 50 33 30 9 3 0 0

Group |
--- | |
Dabrafenib plus trametinib |
Placebo |

Events, n (%) |
--- | |
Dabrafenib plus trametinib 166 (38) |
Placebo 248 (57) |

Median (95% CI), mo |
--- | |
Dabrafenib plus trametinib NR (44.5-NR) |
Placebo 16.6 (12.7-22.1) |

HR (95% CI) |
--- | |
Dabrafenib plus trametinib 0.47 (0.39-0.58); P < .001 |

P = .0000000000000153

No. at Risk
Dabrafenib plus trametinib 438 413 405 392 382 373 355 336 325 299 282 276 263 257 233 202 194 147 116 110 66 52 42 19 7 2 0
Placebo 432 387 322 280 263 243 219 203 198 185 178 175 168 166 158 141 138 106 87 86 50 33 30 9 3 0 0

NR, not reached.
## OVERALL SURVIVAL (FIRST INTERIM ANALYSIS)

### Proportion Alive

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

![Graph showing overall survival rates](image)

### Months From Randomization

<table>
<thead>
<tr>
<th>Group</th>
<th>Events, n (%)</th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib plus trametinib</td>
<td>60 (14)</td>
<td>NR (NR-NR)</td>
<td>0.57 (0.42-0.79); P = .0006^a</td>
</tr>
<tr>
<td>Placebo</td>
<td>93 (22)</td>
<td>NR (NR-NR)</td>
<td></td>
</tr>
</tbody>
</table>

### No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Months From Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib plus trametinib</td>
<td>438 426 416 414 408 401 395 387 381 376 370 366 362 352 328 301 291 233 180 164 105 82 67 28 12 5</td>
</tr>
<tr>
<td>Placebo</td>
<td>432 425 415 410 401 386 378 362 346 337 328 323 308 303 284 269 252 202 164 152 94 64 51 17 7 1</td>
</tr>
</tbody>
</table>

^a Prespecified significance boundary (P = .000019).
Conclusions: Metastatic

• Monotherapy or combination immunotherapy are both appropriate options for all patients

• Anti-PD1 is better than anti-CTLA4
  – Improved RR, PFS and OS
  – Less toxicity
  – Combination anti-CTLA4 and anti-PD1 has higher RR and PFS compared to anti-PD1 but not improved OS and higher toxicity
Conclusions: Adjuvant Therapy

- IFN is in retirement phase
- Ipilimumab high-dose is FDA-approved but should not be used
- PD-1 beats ipilimumab
- BRAF/MEK combo for BRAF+ patients