Immune checkpoint inhibition in melanoma

John Haanen
Immune Checkpoint inhibitors

• Immune checkpoints play an important role in immune tolerance
• Cancer hijacks many of these peripheral tolerance mechanism to escape the immune system
• Inhibition of a single immune checkpoint can be enough to break this cancer induced tolerance (anti-CTLA4, anti-PD-1/PD-L1)
• Combination of these inhibitors appear more powerful
“Melanoma has become from a disease that gave cancer a bad name to a ‘model’ disease for I-O”

Current I-O treatment options for melanoma

– **Stage III disease**
  - Neo-adjuvant/adjuvant trials
– Unresectable stage IIIc and stage IV disease
Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

EORTC 18071/CA184-029: Study Design

Randomized, double-blind, phase 3 study evaluating the efficacy and safety of ipilimumab in the adjuvant setting for high-risk melanoma

Enrollment Period: June 2008 to July 2011

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

N = 951

High-risk, stage III, completely resected melanoma

R

N = 475

INDUCTION
Ipilimumab 10 mg/kg Q3W × 4

MAINTENANCE
Ipilimumab 10 mg/kg Q12W up to 3 years

INFLATION
Placebo Q3W × 4

MAINTENANCE
Placebo Q12W up to 3 years

N = 951

N = 476

Week 1

Week 12

Week 24

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

Q3W = every 3 weeks; Q12W = every 12 weeks; R = randomization.
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab (n = 475)</th>
<th>Placebo (n = 476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>Male, %</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>ECOG PS 0/1, %</td>
<td>94/6</td>
<td>94/6</td>
</tr>
<tr>
<td>Stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>IIIB</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>IIIC with 1-3 positive LN</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>IIIC with ≥4 positive LN</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>1 vs 2-3 vs ≥4 positive LN, %</td>
<td>46 vs 34 vs 20</td>
<td>46 vs 33 vs 21</td>
</tr>
<tr>
<td>LN involvement, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>Macroscopic</td>
<td>56</td>
<td>59</td>
</tr>
<tr>
<td>Ulceration of primary, %</td>
<td>41</td>
<td>43</td>
</tr>
</tbody>
</table>

ECOG PS = Eastern Cooperative Oncology Group performance status; LN = lymph node.
Patients Alive and Without Recurrence (%)

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>264/475</td>
<td>323/476</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.64, 0.89)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>Median RFS, months (95% CI)</td>
<td>27.6 (19.3, 37.2)</td>
<td>17.1 (13.6, 21.6)</td>
</tr>
</tbody>
</table>

RFS (per IRC)

Stratified by stage provided at randomization.
CI = confidence interval.
OS

Stratified by stage provided at randomization.

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

Stratified by stage provided at randomization.

OS

65%

54%

Patients Alive (%)

Number of patients at risk

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>162</td>
<td>475</td>
<td>431 369 325 290 199 62 4</td>
</tr>
<tr>
<td>214</td>
<td>476</td>
<td>413 348 297 273 178 58 8</td>
</tr>
</tbody>
</table>
## Patient Disposition and Treatment

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab (n = 471)</th>
<th>Placebo (n = 474)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation, %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Reasons for discontinuation, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal completion (received study drug for entire 3 years)</td>
<td>13.4</td>
<td>30.2</td>
</tr>
<tr>
<td>Disease recurrence</td>
<td>28.7</td>
<td>59.5</td>
</tr>
<tr>
<td>AE related to study drug</td>
<td>49.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Other reasons^</td>
<td>8.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Median doses, per patient, n</td>
<td>4.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Receiving ≥1 maintenance dose, %</td>
<td>42.0</td>
<td>70.0</td>
</tr>
<tr>
<td>Receiving ≥7 doses (1 year of therapy), %</td>
<td>28.9</td>
<td>56.8</td>
</tr>
</tbody>
</table>

^Includes AE unrelated to study drug, both related and unrelated to study drug, patient request, poor/noncompliance, death, pregnancy, patient no longer eligible, other.
Phase III trials in the adjuvant setting for stage III and IV disease

- A Phase 3, Randomized, Double-blind Study of **Adjuvant** Immunotherapy With **Nivolumab** Versus **Ipilimumab** After Complete Resection of Stage IIIb/c or Stage IV **Melanoma** in Subjects Who Are at High Risk for Recurrence (CheckMate-238)

- **Adjuvant** Immunotherapy With Anti-PD-1 Monoclonal Antibody **Pembrolizumab** Versus **Placebo** After Complete Resection of High-risk Stage III Melanoma: A Randomized, Double-Blind Phase 3 Trial of the EORTC **Melanoma** Group (KEYNOTE-054)

- A Phase III Randomized Trial Comparing Physician/Patient Choice of Either **High Dose Interferon** or **Ipilimumab** to **Pembrolizumab** in Patients With High Risk Resected **Melanoma**
Adjuvant Therapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage III/IV Melanoma: A Randomized, Double-blind, Phase 3 Trial (CheckMate 238)

Jeffrey Weber, 1 Mario Mandala, 2 Michele Del Vecchio, 3 Helen Gogas, 4 Ana M. Arance, 5
C. Lance Cowey, 6 Stéphane Dalle, 7 Michael Schenker, 8 Vanna Chiarion-Sileni, 9 Ivan Marquez-Rodas, 10
Jean-Jacques Grob, 11 Marcus Butler, 12 Mark R. Middleton, 13 Michele Maio, 14 Victoria Atkinson, 15
Paola Queirolo, 16 Veerle de Pril, 17 Anila Qureshi, 17 James Larkin, 18* Paolo A. Ascierto 19*

1 NYU Perlmutter Cancer Center, New York, New York, USA; 2 Papa Giovanni XIII Hospital, Bergamo, Italy; 3 Medical Oncology, National Cancer Institute, Milan, Italy; 4 University of Athens, Athens, Greece; 5 Hospital Clínico de Barcelona, Barcelona, Spain; 6 Texas Oncology-Baylor Cancer Center, Dallas, Texas, USA; 7 Hospices Civils de Lyon, Pierre Bénite, France; 8 Oncology Center SF Nectarie Ltd., Craiova, Romania; 9 Oncology Institute of Veneto IRCCS, Padua, Italy; 10 General University Hospital Gregorio Marañón, Madrid, Spain; 11 Hôpital de la Timone, Marseille, France; 12 Princess Margaret Cancer Centre, Toronto, Ontario, Canada; 13 Churchill Hospital, Oxford, United Kingdom; 14 Center for Immuno-Oncology, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; 15 Gallipoli Medical Research Foundation and Princess Alexandra Hospital, Woolloongabba, and University of Queensland, Greenslopes, Queensland, Australia; 16 IRCCS San Martino-IST, Genova, Italy; 17 Bristol-Myers Squibb, Princeton, New Jersey, USA; 18 Royal Marsden NHS Foundation Trust, London, UK; 19 Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; * Contributed equally to this study.
CA209-238: Study Design

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

1:1

n = 453

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

n = 453
Study Overview

Primary endpoint

- RFS: time from randomization until first recurrence (local, regional, or distant metastasis), new primary melanoma, or death

Secondary endpoints

- OS
- Safety and tolerability
- RFS by PD-L1 tumor expression
- HRQoL

Current interim analysis

- Primary endpoint (RFS), safety, and HRQoL
  - DMFS (exploratory)
- Duration of follow-up: minimum 18 months; 360 events

DMFS = distant metastasis-free survival; HRQoL = health-related quality of life
Most of the patients had cutaneous melanoma (85%), and 4% had acral and 3% had mucosal melanoma.

All 905 patients are off treatment; median doses were 24 (1-26) in the NIVO group and 4 (1-7) in the IPI group.

397 patients completed 1 year of treatment (61% of the NIVO group and 27% of the IPI group).

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NIVO (n = 453)</th>
<th>IPI (n = 453)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>Male, %</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>Stage, IIIB+IIIC, %</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Macroscopic lymph node involvement (% of stage IIIB+IIIC)</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>Ulceration (% of stage IIIB+IIIC)</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>Stage IV, %</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>M1c without brain metastases (% stage IV)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>PD-L1 expression ≥5%, %</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>BRAF mutation, %</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>LDH ≤ ULN, %</td>
<td>91</td>
<td>91</td>
</tr>
</tbody>
</table>
Primary Endpoint: RFS

<table>
<thead>
<tr>
<th></th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>154/453</td>
<td>206/453</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>NR (16.6, NR)</td>
</tr>
<tr>
<td>HR (97.56% CI)</td>
<td>0.65 (0.51, 0.83)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>453</td>
<td>399</td>
<td>364</td>
</tr>
<tr>
<td>353</td>
<td>353</td>
<td>314</td>
</tr>
<tr>
<td>332</td>
<td>332</td>
<td>269</td>
</tr>
<tr>
<td>311</td>
<td>311</td>
<td>252</td>
</tr>
<tr>
<td>291</td>
<td>291</td>
<td>225</td>
</tr>
<tr>
<td>249</td>
<td>249</td>
<td>184</td>
</tr>
<tr>
<td>71</td>
<td>71</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Subgroup Analysis of RFS: PD-L1 Expression Level

<table>
<thead>
<tr>
<th>PD-L1 Expression Level &lt;5%</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>114/275</td>
<td>143/286</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>15.9 (10.4, NR)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.71 (0.56, 0.91)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1 Expression Level ≥5%</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>31/152</td>
<td>57/154</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.50 (0.32, 0.78)</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Number of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIVO</td>
</tr>
<tr>
<td>0</td>
<td>275</td>
</tr>
<tr>
<td>1</td>
<td>242</td>
</tr>
<tr>
<td>3</td>
<td>204</td>
</tr>
<tr>
<td>6</td>
<td>189</td>
</tr>
<tr>
<td>9</td>
<td>171</td>
</tr>
<tr>
<td>12</td>
<td>159</td>
</tr>
<tr>
<td>15</td>
<td>129</td>
</tr>
<tr>
<td>18</td>
<td>41</td>
</tr>
<tr>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
</tr>
</tbody>
</table>

Number of patients at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Number of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIVO</td>
</tr>
<tr>
<td>0</td>
<td>152</td>
</tr>
<tr>
<td>3</td>
<td>135</td>
</tr>
<tr>
<td>6</td>
<td>130</td>
</tr>
<tr>
<td>9</td>
<td>125</td>
</tr>
<tr>
<td>12</td>
<td>122</td>
</tr>
<tr>
<td>15</td>
<td>114</td>
</tr>
<tr>
<td>18</td>
<td>105</td>
</tr>
<tr>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
</tr>
</tbody>
</table>
## RFS: Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of events/no. of patients</th>
<th>Unstratified HR (95% CI)</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIVO 3 mg/kg</td>
<td>IPI 10 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Overall</td>
<td>154/453</td>
<td>206/453</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>106/333</td>
<td>147/339</td>
<td>0.65 (0.51, 0.84)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>48/120</td>
<td>59/114</td>
<td>0.66 (0.45, 0.97)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>99/258</td>
<td>133/269</td>
<td>0.68 (0.53, 0.88)</td>
</tr>
<tr>
<td>Female</td>
<td>55/195</td>
<td>73/184</td>
<td>0.63 (0.44, 0.89)</td>
</tr>
<tr>
<td>Stage (CRF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>41/163</td>
<td>54/148</td>
<td>0.67 (0.44, 1.00)</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>79/204</td>
<td>109/218</td>
<td>0.65 (0.49, 0.87)</td>
</tr>
<tr>
<td>Stage IV M1a-M1b</td>
<td>25/62</td>
<td>35/66</td>
<td>0.63 (0.38, 1.05)</td>
</tr>
<tr>
<td>Stage IV M1c</td>
<td>8/20</td>
<td>8/21</td>
<td>1.00 (0.37, 2.66)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1/2</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>Stage III: Ulceration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>58/201</td>
<td>94/216</td>
<td>0.59 (0.42, 0.82)</td>
</tr>
<tr>
<td>Present</td>
<td>60/153</td>
<td>64/135</td>
<td>0.73 (0.51, 1.04)</td>
</tr>
<tr>
<td>Not reported</td>
<td>2/15</td>
<td>5/15</td>
<td>0.39 (0.07, 2.00)</td>
</tr>
<tr>
<td>Stage III: Lymph node involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic</td>
<td>41/125</td>
<td>55/134</td>
<td>0.71 (0.47, 1.07)</td>
</tr>
<tr>
<td>Macroscopic</td>
<td>72/219</td>
<td>101/214</td>
<td>0.62 (0.46, 0.84)</td>
</tr>
<tr>
<td>Not reported</td>
<td>7/25</td>
<td>7/18</td>
<td>0.60 (0.21, 1.72)</td>
</tr>
<tr>
<td>PD-L1 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%/indeterminate</td>
<td>123/300</td>
<td>149/299</td>
<td>0.71 (0.56, 0.90)</td>
</tr>
<tr>
<td>≥5%</td>
<td>31/152</td>
<td>57/154</td>
<td>0.50 (0.32, 0.78)</td>
</tr>
<tr>
<td>BRAF mutation status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant</td>
<td>63/187</td>
<td>84/194</td>
<td>0.72 (0.52, 1.00)</td>
</tr>
<tr>
<td>Wild-type</td>
<td>67/197</td>
<td>105/214</td>
<td>0.58 (0.43, 0.79)</td>
</tr>
<tr>
<td>Not reported</td>
<td>24/69</td>
<td>17/45</td>
<td>0.83 (0.45, 1.54)</td>
</tr>
</tbody>
</table>
Exploratory Endpoint: DMFS for Stage III Patients

<table>
<thead>
<tr>
<th></th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>93/369</td>
<td>115/366</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.55, 0.95)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>0.0204</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>369</td>
<td>366</td>
</tr>
<tr>
<td>3</td>
<td>335</td>
<td>312</td>
</tr>
<tr>
<td>6</td>
<td>309</td>
<td>284</td>
</tr>
<tr>
<td>9</td>
<td>292</td>
<td>254</td>
</tr>
<tr>
<td>12</td>
<td>280</td>
<td>239</td>
</tr>
<tr>
<td>15</td>
<td>264</td>
<td>217</td>
</tr>
<tr>
<td>18</td>
<td>214</td>
<td>176</td>
</tr>
<tr>
<td>21</td>
<td>62</td>
<td>51</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

DMFS (%) vs. Months

- NIVO
- IPI
Treatment-Related Select Adverse Events

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>NIVO (n = 452)</th>
<th>IPI (n = 453)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Skin</td>
<td>201 (44.5)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>114 (25.2)</td>
<td>9 (2.0)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>41 (9.1)</td>
<td>8 (1.8)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>6 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>6 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity/infusion reaction</td>
<td>11 (2.4)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal disorder</td>
<td>6 (1.3)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pituitary disorder</td>
<td>8 (1.8)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>92 (20.4)</td>
<td>3 (0.7)</td>
</tr>
</tbody>
</table>

- Median time to onset of treatment-related select AEs was generally shorter for patients receiving IPI (range 2.6-10 weeks) than for those receiving NIVO (range 3.3-14.2 weeks)
Conclusions

• Nivolumab showed a clinically and statistically significant improvement in RFS vs the active control of high-dose ipilimumab for patients with resected stages IIIB/IIIC and stage IV melanoma at high risk of recurrence (HR = 0.65, \( P < 0.0001 \))
  – 18-month RFS rates were 66% for nivolumab and 53% for ipilimumab
  – Benefit for nivolumab was observed across the majority of prespecified subgroups tested, including PD-L1 and BRAF mutation status

• Nivolumab has a superior safety profile in comparison with ipilimumab, with fewer grade 3/4 AEs and fewer AEs leading to treatment discontinuation

• Nivolumab has the potential to be a new standard treatment option for patients with resected stage IIIB, IIIC, and IV melanoma regardless of BRAF mutation
New developments in adjuvant and neoadjuvant trials

• An Open-label, Phase IB Study of NEO-PV-01 + Adjuvant With Nivolumab in Patients With Melanoma, Non-Small Cell Lung Carcinoma or Transitional Cell Carcinoma of the Bladder

• Phase II Study to Identify the Optimal neoadjuvant Combination Scheme of Ipilimumab and Nivolumab in Stage III Melanoma Patients (OPACIN-neo)

• A Phase II, Randomised, Open Label Study of Neoadjuvant Dabrafenib, Trametinib and / or Pembrolizumab in BRAF V600 Mutant Resectable Stage IIIB/C Melanoma

• A Phase 1b Trial of Neoadjuvant CXCR4 antagonist (X4P-001) Alone and With Pembrolizumab in Patients With Resectable Melanoma
“Melanoma has become from a disease that gave cancer a bad name to a ‘model’ disease for I-O”

Current I-O treatment options for melanoma

– Stage III disease
  • Neo-adjuvant/adjuvant trials

– Unresectable stage IIIc and stage IV disease
Anti-CTLA-4
Ipilimumab: 4 infusions for the induction

Pre-treated-pts
+/- gp100
HLA-A2
3mg/kg
Re-induction possible

naive-pts
+ DTIC
10 mg/kg
Maintenance possible

Hodi et al 2010 NEJM

Robert et al NEJM 2011
Pooled OS Analysis of ipilimumab treated 4846 patients (incl EAP)

Median OS (95% CI): 9.5 (9.0–10.0)

3-year OS rate (95% CI): 21% (20–22%)

Schadendorf et al., J Clin Oncol 2015
Anti-PD1 Demonstrates Broad Antitumor Activity

![Graphs showing change from baseline in tumor size% for various tumors](attachment://graphs.png)


Courtesy of G Long
CheckMate-066

Unresectable or metastatic melanoma
- Previously untreated
- BRAF wild-type
- Tissue available for PD-L1 testing

Randomize 1:1

Nivolumab 3 mg/kg IV every 2 weeks + Placebo IV every 3 weeks

Dacarbazine 1000 mg/m² IV every 3 weeks + Placebo IV every 2 weeks

Treat until progression or unacceptable toxicity
Primary endpoint: Overall survival

Robert et al., NEJM 2015
Updated OS results from CheckMate 066 trial in BRAF wt advanced melanoma

Decrease of the risk of death 58% vs chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>NIVO (N = 210)</th>
<th>DTIC (N = 208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>NR</td>
<td>11.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(23.1, NR)</td>
<td>(9.6, 13.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.43 (0.33, 0.57); P &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Cl = confidence interval, HR = hazard ratio; mo = month

Atkinson et al. abstract 3774 SMR 2015
OS after ipilimumab start as 2nd line treatment

NIVO to IPI

Median OS, mo
(95% CI)
9.0
(7.1, 14.7)

Probability of Survival

Months

Number of Patients at Risk

<table>
<thead>
<tr>
<th>NIVO to IPI</th>
<th>57</th>
<th>46</th>
<th>35</th>
<th>24</th>
<th>19</th>
<th>11</th>
<th>7</th>
<th>3</th>
<th>0</th>
</tr>
</thead>
</table>

Cl = confidence interval; mo = month
Pembrolizumab vs ipilimumab

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 12 mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab Q2W</td>
<td>NR (NR-NR)</td>
<td>74.1%</td>
<td>0.63 (0.47-0.83)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Pembrolizumab Q3W</td>
<td>NR (NR-NR)</td>
<td>68.4%</td>
<td>0.69 (0.52-0.90)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>NR (12.7-NR)</td>
<td>58.2%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Decrease of risk of death of pembrolizumab 31 to 37% vs ipilimumab
ANALYSIS OF RESPONSE AND SURVIVAL IN PATIENTS WITH IPILIMUMAB-REFRACTORY MELANOMA TREATED WITH PEMBROLIZUMAB IN KEYNOTE-002

A. Daud¹; I. Puzanov²; R. Dummer³; D. Schadendorf⁴; O. Hamid⁵; C. Robert⁶; F. S. Hodi⁷; J. Schachter⁸; J. A. Sosman⁹; A. C. Pavlick¹⁰; R. Gonzalez¹¹; C. Blank¹²; L. D. Cranmer¹³; S. J. O’Day¹⁴; A. K. Salama¹⁵; K. A. Margolin¹⁶; J. Yang¹⁷; B. Homet Moreno¹⁷; N. Ibrahim¹⁷; A. Ribas¹⁸

¹University of California, San Francisco, San Francisco, CA, USA; ²Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; (currently at Roswell Park Cancer Institute, Buffalo, NY, USA; ³University of Zürich, Zürich, Switzerland; ⁴University Hospital Essen, Essen, Germany; ⁵The Angeles Clinic and Research Institute, Los Angeles, CA, USA; ⁶Gustave Roussy and Paris-Sud University, Villejuif, France; ⁷Dana-Farber Cancer Institute, Boston, MA, USA; ⁸Ella Lemberg Institute of Melanoma, Sheba Medical Center, Tel Hashomer, Israel; ⁹Vanderbilt-Ingram Cancer Center, Nashville, TN, USA (currently at Northwestern University Feinberg School of Medicine, Chicago, IL, USA, USA); ¹⁰New York University Cancer Institute, New York, NY, USA; ¹¹University of Colorado Denver, Aurora, CO, USA; ¹²Netherlands Cancer Institute, Amsterdam, Netherlands; ¹³currently at University of Washington and Seattle Cancer Care Alliance, Seattle, WA, USA; ¹⁴John Wayne Cancer Institute, Santa Monica, CA, USA; ¹⁵Duke Cancer Institute, Durham, NC, USA; ¹⁶City of Hope, Duarte, CA, USA; ¹⁷Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; ¹⁸University of California, Los Angeles, Los Angeles, CA, USA
Time to and Duration (RECIST v1.1, INV) of Complete Response to Pembrolizumab

Patients with CR, n = 29

<table>
<thead>
<tr>
<th></th>
<th>Median, mo (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to CR</td>
<td>2.9 (2.4-24.9)</td>
</tr>
<tr>
<td>Time from SD to CR (n = 5)</td>
<td>6.9 (3.9-21.9)</td>
</tr>
<tr>
<td>Time from PR to CR (n = 21)</td>
<td>8.0 (1.4-25.2)</td>
</tr>
<tr>
<td>Duration of CR</td>
<td>Not reached (5.5-41.6+)</td>
</tr>
</tbody>
</table>

Arrows indicate conversion from SD to CR; 5 patients converted from SD and 21 from PR to CR. Median DOR in all treated patients was not reached (range 1.9+ mo to 43.5+ mo). Of 20 patients without PD, 14 discontinued because of AEs (n = 3) or patient/physician decision (n = 11). Data cut-off: February 3, 2017.
Time to and Duration (RECIST v1.1, INV) of Partial Response to Pembrolizumab

**Patients with PR, n = 70**

<table>
<thead>
<tr>
<th>Time to PR</th>
<th>Median, mo (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>2.9 (1.9-27.9)</td>
</tr>
<tr>
<td>Time from SD to PR (n = 28)</td>
<td>2.7 (0.9-25.2)</td>
</tr>
<tr>
<td>Duration of PR</td>
<td>Not reached (1.9+ to 43.5+)</td>
</tr>
</tbody>
</table>

**Patients with SD, n = 88**

<table>
<thead>
<tr>
<th>Median, mo (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aDuration of SD</td>
</tr>
</tbody>
</table>

Arrows indicate conversion from SD to PR; 28 patients converted from SD to PR.
Median DOR in all treated patients was not reached (range 1.9+ mo to 43.5+ mo).
Of 25 patients without PD, 24 discontinued because of AEs (n = 11) or physician/patient decision (n = 13).
PFS AND OS in All Pembrolizumab-Treated Patients and Those With Best Response of CR, PR, or SD

<table>
<thead>
<tr>
<th>Group</th>
<th>Events, n</th>
<th>Median, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>29</td>
<td>41.0 (38.9-NR)</td>
</tr>
<tr>
<td>PR</td>
<td>70</td>
<td>35.8 (27.9-NR)</td>
</tr>
<tr>
<td>SD</td>
<td>88</td>
<td>7.0 (5.8-9.7)</td>
</tr>
<tr>
<td>All treated</td>
<td>361</td>
<td>4.2 (3.3-5.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Events, n</th>
<th>Median, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>29</td>
<td>NR (NR-NR)</td>
</tr>
<tr>
<td>PR</td>
<td>70</td>
<td>NR (NR-NR)</td>
</tr>
<tr>
<td>SD</td>
<td>88</td>
<td>16.5 (13.8-20.5)</td>
</tr>
<tr>
<td>All treated</td>
<td>361</td>
<td>14.0 (11.8-16.2)</td>
</tr>
</tbody>
</table>

NR, not reached.
PFS was assessed by RECIST v1.1 per investigator.
Conclusions

• Responses to pembrolizumab are durable and associated with prolonged OS in ipilimumab-refractory melanoma

• Even in these heavily pretreated patients, best response can evolve over time, with late conversions from SD to PR/CR and PR to CR observed

• No new safety signals with longer term follow-up
Keynote 001: phase I study of pembrolizumab in 655 metastatic melanoma patients. Median follow-up of 43 months

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>

Overall Survival, %

No. at risk

| 655 | 516 | 424 | 370 | 318 | 290 | 238 | 134 | 54 | 5 | 0 |

Treatment Naive\textsuperscript{a}

<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>

Overall Survival, %

No. at risk

| 152 | 127 | 109 | 98 | 90 | 85 | 68 | 39 | 15 | 0 | 0 |

\textsuperscript{a}Excludes patients with ocular melanoma. Analysis cutoff date: September 1, 2016.

Robert et al EADO 2017
Pembrolizumab phase 1: Keynote 001: Median Follow-Up 43 Months for 655 patients

Consent withdrawal 5%
Discontinue for physician Decision 11%
Discontinued for AEs: 25%
Discontinued for PD: 42%
On treatment: 16%

Range of follow-up: 36-57 months.
Analysis cutoff date: September 1, 2016.

Robert et al EADO 2017
Complete Responders: Disposition
Median follow-up: 43 months

- 92 (88%) remained in CR
- 105 (16%) patients had CR per irRC by investigator review
- 14 (13%) remained on pembrolizumab
- 24 (23%) discontinued for AEs (n = 12), PD (n = 2), or other reason (n = 10)
- 67 (64%) stopped pembrolizumab for observation

*Patient was alive and without disease progression.
Analysis cutoff date: September 1, 2016.
Complete Responders Who Stopped Pembrolizumab for Observation (N = 67)

- Median time to CR: 13 mo (3-36 mo)
- 61 (91%) responses were maintained
- Median response duration: NR (6+ to 56+ mo)

Total bar length represents the time to the last scan.
Analysis cutoff date: September 1, 2016.
Complete Responders Who Stopped Pembrolizumab for Observation (N = 67)

- 2 patients died; causes unrelated to pembrolizumab (3, 6)
- Only 4 patients experienced PD
  - 2 received commercial pembrolizumab, and had PD (1, 4)
  - 2 received 2nd course pembrolizumab
    - 1 had PR and is ongoing (2)
    - 1 had PD (5)

Total bar length represents the time to the last scan.
Analysis cutoff date: September 1, 2016.

Robert et al EADO 2017
How long to treat with anti-PD1?

In case of a partial response or stable disease?
KEYNOTE-006 (NCT01866319) Study Design

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

**Treatment Arms**
- **Pembrolizumab**
  - 10 mg/kg intravenous Q2W for 2 years

- **Pembrolizumab**
  - 10 mg/kg intravenous Q3W for 2 years

- **Ipilimumab**
  - 3 mg/kg intravenous Q3W × 4 doses

*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.*

*Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).*
Keynote 006: Patients Who Completed Protocol-Specified Time on Pembrolizumab\textsuperscript{a} (median follow-up, 9.7 mo)

556 patients received pembrolizumab

104 (19\%) completed pembrolizumab

- 24 (23\%) CR
  - 23 ongoing responses
  - 1 PD\textsuperscript{b}
    - 1 received second course of pembrolizumab

- 68 (65\%) PR
  - 64 ongoing responses
  - 4 PD\textsuperscript{b}
    - 3 received second course of pembrolizumab

- 12 (12\%) SD
  - 10 ongoing SD
  - 2 deaths\textsuperscript{b,c}

\textsuperscript{a}Includes patients completing ≥21.6 months of treatment.

\textsuperscript{b}From end of pembrolizumab treatment.

\textsuperscript{c}Both deaths were a result of PD. Data cutoff date: Nov 3, 2016.
PFS (irRC, investigator) from last Pembrolizumab dose in patients who completed protocol-specified time on treatment (n = 104)

102 (98%) patients were alive after a median of 9.7 months after completing pembrolizumab treatment
Do we treat for too long? What is the risk?

Late Adverse events with anti-PD1?

Weber et al. J Clin Oncol 2017
No Significant increase in AE incidence between 2 and 3 years with anti-PD1

TREATMENT-RELATED AE INCIDENCE OVER TIME

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Pembrolizumab N = 555</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median FU (months)</td>
<td>7.9</td>
</tr>
<tr>
<td>Any grade %</td>
<td>76.2</td>
</tr>
<tr>
<td>Grade ¾ %</td>
<td>11.7</td>
</tr>
<tr>
<td>Led to death %</td>
<td>0</td>
</tr>
<tr>
<td>Led to discontinuation %</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Data from Ribas et al, AACR 2015; Robert et al ASCO 2016; Robert et al ASCO 2017

Analysis includes all randomized patients who received ≥1 pembrolizumab dose.

aAs designated by the investigator. bBecause of sepsis.

Data cutoff date: Nov 3, 2016.
When can we stop anti-PD1?
Help from PFS curve

Ugurel S et al Eur J Cancer 2017
Keynote 006 PFS Total Population (Median Follow-Up, 33.9 mo)

Progression-Free Survival, %

No. at risk

<table>
<thead>
<tr>
<th>Time, months</th>
<th>Pembrolizumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>556</td>
<td>278</td>
</tr>
<tr>
<td>4</td>
<td>347</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>269</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>231</td>
<td>40</td>
</tr>
<tr>
<td>16</td>
<td>211</td>
<td>32</td>
</tr>
<tr>
<td>20</td>
<td>182</td>
<td>27</td>
</tr>
<tr>
<td>24</td>
<td>155</td>
<td>23</td>
</tr>
<tr>
<td>28</td>
<td>138</td>
<td>20</td>
</tr>
<tr>
<td>32</td>
<td>88</td>
<td>14</td>
</tr>
<tr>
<td>36</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Pembrolizumab
Ipilimumab

C Robert et al  ASCO 2017
Conclusion

• The optimal duration of immunotherapy is presently unknown
• Encouraging data: documentation of long term benefit after discontinuation
  – in CR or after two years of treatment with anti-PD1 monotherapy (pembrolizumab)
• Randomized discontinuation trial needed but challenging to organize
• Practically: decision should be based upon patient’s clear information and decision
  – In case discontinuation due to toxicity and when the disease is not progressing, we advise not to rechallenge
  – In case of confirmed CR after at least 6 months of therapy, if patients agree, we propose to stop
  – In case of PR or SD, if patients agree, we propose to stop after 2 years
Why combining immunotherapies?
Cancer Immunogram

Tumor foreignness
**Mutational load**

Intratumoral T cells

Immune cell infiltration

General immune status
**Lymphocyte count**

Absence of Checkpoints
**PD-L1**

Absence of soluble inhibitors
**IL6-CRP/ESR**

Absence of inhibitory tumor metabolism
**LDH, glucose utilization**

Tumor sensitivity to immune effectors
- **MHC expression**
- **IFN- sensitivity**

Tumor, Haanen et al. Science 2016
Combinations with immunotherapy

Non-immune therapies
- Radiotherapy
- Chemotherapy
- Anti-angiogenic agents
- Targeted therapies (including antitumour cytotoxic mAbs)
- Virotherapy

Hallmark mechanisms of synergy in immunotherapy
- Increased lymphocyte infiltration into tumours
- Immunogenic cell death
- Activation of primed T cells and reversion of exhaustion
- Attenuation of immunosuppression in the tumour microenvironment:
  - $T_{reg}$ cell function
  - Myeloid-derived suppressor cells
  - Immunosuppressive cytokines
  - Immunosuppressive enzymes
- Increased numbers of tumour-specific T cells
- Enhancing the performance of antigen-presenting cells

Immunotherapies
- Immunostimulatory mAbs
  - CTLA4
  - PD1 or PDL1
  - LAG3
  - TIM3
  - CD137
  - OX40
  - GITR
  - CD40
- Neutralizing other immune inhibitors:
  - TGFβ
  - IL-10
  - IDO1
- Activatory cytokines:
  - IFNα
  - IL-2
  - IL-12
- Adoptive T cell therapy
- Cancer vaccines
- Microbiological adjuvants:
  - TLR agonists
  - α-GalCer
  - STING activators

Melero, .., Haanen Nat Rev Canc 2015
Most combinations have anti-PD1/PDL1 as backbone
CheckMate 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:
• BRAF status
• AJCC M stage
• Tumor PD-L1 expression <5% vs ≥5%*

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

Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

*The study was not powered for a comparison between NIVO and NIVO+IPI

Presented at AACR 2017 by Larkin
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
Progression-Free Survival

<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 PFS, mo (95% CI)</td>
<td>11.7 (8.9–21.9)</td>
<td>6.9 (4.3–9.5)</td>
<td>2.9 (2.8–3.2)</td>
</tr>
<tr>
<td>HR (95% CI) vs. IPI</td>
<td>0.42 (0.34–0.51)</td>
<td>0.54 (0.45–0.66)</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.76 (0.62–0.94)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

 Patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>314</td>
<td>218</td>
<td>176</td>
<td>156</td>
</tr>
<tr>
<td>316</td>
<td>178</td>
<td>151</td>
<td>132</td>
</tr>
<tr>
<td>315</td>
<td>136</td>
<td>77</td>
<td>58</td>
</tr>
</tbody>
</table>

Database lock: Sept 13, 2016, minimum f/u of 28 months

Presented at AACR 2017 by Larkin
## Overall Survival

<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>Median OS, mo (95% CI)</strong></td>
<td>NR</td>
<td>NR (29.1–NR)</td>
<td>20.0 (17.1–24.6)</td>
</tr>
<tr>
<td><strong>HR (98% CI) vs. IPI</strong></td>
<td>0.55 (0.42–0.72)*</td>
<td>0.63 (0.48–0.81)*</td>
<td>--</td>
</tr>
<tr>
<td><strong>HR (95% CI) vs. NIVO</strong></td>
<td>0.88 (0.69–1.12)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*P<0.0001

Database lock: Sept 13, 2016, minimum f/u of 28 months

Presented at AACR 2017 by Larkin
Subsequent Therapies: All Randomized Patients

<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>Any subsequent therapy, n (%)*</td>
<td>129 (41)</td>
<td>169 (54)</td>
<td>225 (71)</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>100 (32)</td>
<td>140 (44)</td>
<td>196 (62)</td>
</tr>
<tr>
<td>Anti-PD-1 agents</td>
<td>30 (10)</td>
<td>32 (10)</td>
<td>132 (42)</td>
</tr>
<tr>
<td>Anti-CTLA-4</td>
<td>19 (6)</td>
<td>83 (26)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>BRAF inhibitors</td>
<td>40 (13)</td>
<td>57 (18)</td>
<td>68 (22)</td>
</tr>
<tr>
<td>MEK inhibitors</td>
<td>30 (10)</td>
<td>38 (12)</td>
<td>39 (12)</td>
</tr>
<tr>
<td>Investigational agents**</td>
<td>8 (3)</td>
<td>6 (2)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Median time to subsequent</td>
<td>NR (NR–NR)</td>
<td>26.8 (18.0–NR)</td>
<td>8.5 (7.3–9.7)</td>
</tr>
<tr>
<td>systemic therapy, mo (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 year % of pts free of</td>
<td>65.8</td>
<td>53.8</td>
<td>24.7</td>
</tr>
<tr>
<td>subsequent therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients may have received more than 1 subsequent therapy (e.g. radiation, surgery and systemic therapies)
**Other than investigational immunotherapy, BRAF inhibitors, and MEK inhibitors

Presented at AACR 2017 by Larkin
Outcomes Observed at PDL1 1% Cutoff

PD-L1 Expression Level <1%

<table>
<thead>
<tr>
<th>&lt;1% PD-L1</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–NR)</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>≥1% PD-L1</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

Presented at AACR 2017 by Larkin
Safety Summary

• With an additional 19 months of follow-up, safety was consistent with the initial report\(^1\)

<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>Treatment-related adverse event (AE)</td>
<td>95.8</td>
<td><strong>58.5</strong></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

\(^a\)Cardiomyopathy (NIVO+IPI, n=1); Liver necrosis (NIVO+IPI, n=1). Both deaths occurred >100 days after the last treatment.
\(^b\)Neutropenia (NIVO, n=1); colon perforation (IPI, n=1).\(^1\)

Conclusions

• NIVO+IPI and NIVO significantly improved OS and PFS vs. IPI alone in patients with untreated advanced melanoma

• In descriptive analyses, NIVO+IPI resulted in numerically higher OS, PFS and ORR vs. NIVO alone

• Results consistently favored NIVO+IPI across clinically relevant subgroups, including PD-L1 expression <5% or <1%, mutant BRAF, and elevated LDH
  – Although similar prolongation of OS was observed with NIVO and NIVO+IPI for PD-L1 expression ≥5% or ≥1%, NIVO+IPI resulted in higher ORR regardless of PD-L1 expression

• For NIVO+IPI, median DOR and time to subsequent therapy are still not reached

• The safety profile of the combination showed high rate of grade 3-4 IR toxicity, but early discontinuation due to AEs did not preclude benefit