Melanoma and Immunotherapy

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The Transformed Landscape of Melanoma Therapy: Approved Drugs Before 2011

• **Dacarbazine (DTIC), 1970s**
  – Response rate: <10% in unselected stage IV melanoma patients
  – No proven impact on survival

• **High-dose IL-2, 1998**
  – Response rate: 16% in highly selected stage IV melanoma patients
  – Durable responses: ~5%
  – Rarely used outside of specialized centers
  – Not used outside USA
New Paradigm in the treatment of melanoma: Hit a Target

Immunotherapy

Target host

Targeted Therapy

Target tumor
2015 Approach to Melanoma

- Targeting the immune system
  - Anti CTLA4 (ipilimumab)
  - Anti PD-1 (pembrolizumab, nivolumab)
    - Post ipilimumab
    - Front line
  - Combination Anti CTLA-4/Anti PD-1

- Targeting the tumor pathway
  - MAP kinase targeted therapy (BRAF/MEK)
  - Other targets
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?
T-cell receptor: Antigen-MHC

CD-28: B7

T-Reg

CTLA-4: B7

Ipilimumab
“Check-Point Inhibitor” Inhibitors

• Anti CTLA4 antibody: Ipilimumab
  – Approved for melanoma 2011

• Anti PD-1 inhibitors: nivolumab, pembrolizumab
  – Approved for melanoma and lung cancer 2014, 2015

• Others in Development
2015 Approach to Melanoma

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  – Anti PD-1 (pembrolizumab, nivolumab)
    • Post ipilimumab
    • Front line
  – Combination Anti CTLA-4/Anti PD-1

• Targeting the tumor pathway
  – MAP kinase targeted therapy (BRAF/MEK)
  – Other targets
Ipilimumab Augments T-Cell Activation and Proliferation

Adapted from O'Day et al. Plenary session presentation, abstract #4, ASCO 2010.
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


Ipilimumab (anti CTLA-4) is better than chemotherapy or vaccines
2015 Approach to Melanoma

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  – Anti CTLA4 (ipilimumab)
  – Anti PD-1 (pembrolizumab, nivolumab)
    • Post ipilimumab
    • Front line
  – Combination Anti CTLA-4/Anti PD-1

• Targeting the tumor pathway
  – MAP kinase targeted therapy (BRAF/MEK)
  – Other targets
Role of PD-1 Pathway in Suppressing Anti-tumor Immunity

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells

Tumor cell

Dendritic cell

IFNγR

MHC

T-cell receptor

PD-L1

PD-L2

PD-1

PD-1

PD-1

PD-1

PD-L1

PD-L2

Nivolumab

PD-1 Receptor Blocking Ab

ASCO 2013

Presented By Mario Sznol, MD at 2013 ASCO Annual Meeting
The Future of Melanoma Immunotherapy

**PD1 Blockade**

Reviving Exhausted T Cells
2015 Approach to Melanoma

• Targeting the immune system
  – Anti CTLA4 (ipilimumab)
  – Anti PD-1 (pembrolizumab, nivolumab)
    • Post ipilimumab
    • Front line
  – Combination Anti CTLA-4/Anti PD-1

• Targeting the tumor pathway
  – MAP kinase targeted therapy (BRAF/MEK)
  – Other targets
Pembrolizumab Post-Ipilimumab

Robert et al Lancet 2014
KEYNOTE-002 (NCT01704287): International, Randomized, Pivotal Study

**Patients**
- Advanced melanoma
- PD within 24 weeks after ≥2 IPI doses
- Previous BRAF or MEK inhibitor (if BRAF mutant)
- ECOG PS 0-1
- Resolution of IPI-related AEs
- No chronic systemic steroid therapy (>10 mg/day prednisone or equivalent)
- No active autoimmune disease

**Stratification factors:**
- ECOG PS (0 vs 1)
- LDH (normal vs elevated)
- BRAF status (mutant vs wild type)

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

Ribas et al SMR 2014
Keynote 002: Progression-Free Survival
(Post ipilimumab, RECIST v1.1, Central Review)

Analysis cut-off date: May 12, 2014.

Ribas A et al SMR 2014
After ipilimumab, anti PD-1 is better than chemotherapy
2015 Approach to Melanoma

• Targeting the immune system
  – Anti CTLA4 (ipilimumab)
  – Anti PD-1 (pembrolizumab, nivolumab)
    • Post ipilimumab
    • Front line
  – Combination Anti CTLA-4/Anti PD-1

• Targeting the tumor pathway
  – MAP kinase targeted therapy (BRAF/MEK)
  – Other targets
Phase 3 CA209-066: Study Design

Eligible patients with unresectable stage III or IV melanoma (N=418)
- BRAF wild-type
- Treatment-naïve

Stratified by:
- PD-L1 status (≥ 5% cell-surface staining cutoff)
- M-stage

Double-blind

Nivolumab
3 mg/kg IV Q2W
+ Placebo
IV Q3W
N=210
(206 treated)

Treat until progression* or unacceptable toxicity

Primary endpoint:
- OS

Secondary endpoints:
- PFS
- ORR
- PD-L1 correlates

Placebo
IV Q2W
+ Dacarbazine
1000 mg/m² IV Q3W
N=208
(205 treated)

Long G et al SMR Presentation 2014 Zurich
## Best Overall Response

<table>
<thead>
<tr>
<th>Nivolumab (N=210)</th>
<th>Dacarbazine (N=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>40% (33–47%)</td>
</tr>
</tbody>
</table>

### Best overall response

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Partial response</td>
<td>32%</td>
<td>13%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>17%</td>
<td>22%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>33%</td>
<td>49%</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>11%</td>
<td>15%</td>
</tr>
</tbody>
</table>

*Robert et al NEJM 2014 and Long et al SMR 2014*
Primary Endpoint: OS

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

Patients who died, n/N

Median OS mo (95% CI)

Nivolumab
50/210  NR

DTIC
96/208  10.8 (9.3–12.1)

Follow-up since randomization: 5.2–16.7 months

Long, G et al SMR Presentation 2014 Zurich
Anti PD-1 is better than chemotherapy front-line
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 BRAF status b
- 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 c vs negative)

Pembrolizumab
10 mg/kg IV Q2W

Ipilimumab
3 mg/kg IV Q3W x 4 doses

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

*Patients enrolled from 83 sites in 16 countries.

bPrior 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.

cDefined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.
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 (2.9-6.9)</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 (2.8-2.9)</td>
<td>26.5%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Analysis cut-off date: September 3, 2014.
**OS at the Second Interim Analysis (IA2)**

<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>0.00052</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>0.00358</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>NR (12.7-NR)</td>
<td>58.2%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>279</th>
<th>266</th>
<th>248</th>
<th>233</th>
<th>219</th>
<th>212</th>
<th>177</th>
<th>67</th>
<th>19</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>277</td>
<td>266</td>
<td>251</td>
<td>238</td>
<td>215</td>
<td>202</td>
<td>158</td>
<td>71</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>18 months</td>
<td>278</td>
<td>242</td>
<td>212</td>
<td>188</td>
<td>169</td>
<td>157</td>
<td>117</td>
<td>51</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

Analysis cut-off date: March 3, 2015.
# Tumor Response at the First Interim Analysis (RECIST v1.1, Central Review)

<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>ORR (95% CI)</strong></td>
<td>33.7% (28.2-39.6)</td>
<td>32.9% (27.4-38.7)</td>
<td>11.9% (8.3-16.3)</td>
</tr>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>5.0%</td>
<td>6.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Partial response</td>
<td>28.7%</td>
<td>26.7%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13.3%</td>
<td>14.1%</td>
<td>16.5%</td>
</tr>
<tr>
<td>NonCR/nonPD(a)</td>
<td>4.7%</td>
<td>5.1%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>38.0%</td>
<td>41.2%</td>
<td>48.9%</td>
</tr>
<tr>
<td>Not evaluable(b)</td>
<td>7.2%</td>
<td>5.4%</td>
<td>18.3%</td>
</tr>
<tr>
<td>No assessment(c)</td>
<td>3.2%</td>
<td>1.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td><strong>Ongoing responses</strong></td>
<td>89.4%</td>
<td>96.7%</td>
<td>87.9%</td>
</tr>
<tr>
<td><strong>Median duration of response (range), days</strong></td>
<td>251 (42+ to 251)</td>
<td>NR (42+ to 246+)</td>
<td>NR (33+ to 239+)</td>
</tr>
</tbody>
</table>

\(a\) Patients without measurable disease per central review at baseline who did not experience complete response or disease progression.

\(b\) Target lesion not captured by postbaseline scans or for whom a target lesion was surgically removed.

\(c\) No postbaseline scan performed or were not able to be evaluated.

Analysis cut-off date: September 3, 2014.
Best Percentage Change From Baseline in Target Lesions at IA1 (RECIST v1.1, Central Review)

Analysis cut-off date: September 3, 2014.
Anti PD-1 is better than ipilimumab front line
2015 Approach to Melanoma

• Targeting the immune system
  – Anti CTLA4 (ipilimumab)
  – Anti PD-1 (pembrolizumab, nivolumab)
    • Post ipilimumab
    • Front line
  – Combination Anti CTLA-4/Anti PD-1

• Targeting the tumor pathway
  – MAP kinase targeted therapy (BRAF/MEK)
  – Other targets
Blocking CTLA-4 and PD-1

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)

Tumor Microenvironment

Activation
(cytokines, lysis, proliferation, migration to tumor)
Improved Clinical Response in Patients With Advanced Melanoma Treated With Nivolumab Combined With Ipilimumab Compared With Ipilimumab Alone


1Dana-Farber Cancer Institute, Boston, MA, USA; 2Ludwig Center at Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3University of Louisville, Louisville, KY, USA; 4New York University, New York, NY, USA; 5Gustave, Roussy and INSERM U981, Villejuif-Paris-Sud, France; 6Huntsman Cancer Institute, Salt Lake City, UT, USA; 7Beth Israel Deaconess Medical Center, Boston, MA, USA; 8Washington University, St Louis, MO, USA; 9Institut Universitaire du Cancer, Toulouse, France; 10Greenville Health System, Greenville, SC, USA; 11St Luke's Cancer Center and Temple University, Bethlehem, PA, USA; 12University of New Mexico, Albuquerque, NM, USA; 13Dartmouth Hitchcock Medical Center, Lebanon, NH, USA; 14California Pacific Center for Melanoma Research, San Francisco, CA, USA; 15Duke University, Durham, NC, USA; 16Oregon Health & Science University, Portland, OR, USA; 17Bristol-Myers Squibb, Wallingford, CT, USA; 18Bristol-Myers Squibb, Lawrenceville, NJ, USA
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

Treat until progression** or unacceptable toxicity

N=316

NIVO 3 mg/kg Q2W + IPI-matched placebo

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.
PFS (Intent-to-Treat)

<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, months (95% CI)</td>
<td>11.5 (8.9–16.7)</td>
<td>6.9 (4.3–9.5)</td>
<td>2.9 (2.8–3.4)</td>
</tr>
<tr>
<td>HR (99.5% CI) vs. IPI</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.57 (0.43–0.76)*</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.74 (0.60–0.92)**</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Stratified log-rank P<0.00001 vs. IPI
**Exploratory endpoint
## Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong>*</td>
<td>57.6 (52.0–63.2)</td>
<td>43.7 (38.1–49.3)</td>
<td>19.0 (14.9–23.8)</td>
</tr>
<tr>
<td>Two-sided <em>P</em> value vs IPI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td><strong>Best overall response — %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>11.5</td>
<td>8.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>46.2</td>
<td>34.8</td>
<td>16.8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13.1</td>
<td>10.8</td>
<td>21.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22.6</td>
<td>37.7</td>
<td>48.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.7</td>
<td>7.9</td>
<td>10.2</td>
</tr>
<tr>
<td><strong>Duration of response (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR (13.1, NR)</td>
<td>NR (11.7, NR)</td>
<td>NR (6.9, NR)</td>
</tr>
</tbody>
</table>

*By RECIST v1.1.
NR, not reached.
Safety Summary

<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>95.5</td>
<td>55.0</td>
<td>82.1</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>36.4</td>
<td>29.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Treatment-related death*</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response.
Combination anti ipilimumab and anti PD-1 is better than ipilimumab and maybe better than anti PD-1
2015 Approach to Melanoma

• Targeting the immune system
  – Anti CTLA4 (ipilimumab)
  – Anti PD-1 (pembrolizumab, nivolumab)
    • Post ipilimumab
    • Front line
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• Targeting the tumor pathway
  – MAP kinase targeted therapy (BRAF/MEK)
  – Other targets
MAPK Pathway

Growth Factors

- RAS
- BRAF
- MEK
- ERK

Cell proliferation and survival
BRAF Mutation

Growth Factors

RAS

BRAF

MEK

ERK

Increased cell proliferation and survival

BRAF mutation is present in ~50% of melanomas
FDA Approved BRAF Inhibitors

<table>
<thead>
<tr>
<th>IC50</th>
<th>vemurafenib</th>
<th>dabrafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt BRAF</td>
<td>39nM</td>
<td>3.2nM</td>
</tr>
<tr>
<td>CRAF</td>
<td>16nM</td>
<td>5nM</td>
</tr>
<tr>
<td>V600E BRAF</td>
<td>8nM</td>
<td>0.65nM</td>
</tr>
<tr>
<td>V600K BRAF</td>
<td>NR</td>
<td>0.5nM</td>
</tr>
<tr>
<td>V600D BRAF</td>
<td>NR</td>
<td>1.84nM</td>
</tr>
</tbody>
</table>
Phase III BRIM3 trial: Study design

Screening

BRAF<sup>V600E</sup> mutation

Stratification
- Stage
- ECOG PS (0 vs 1)
- LDH elevated vs normal
- Geographic region

Randomization N=675

Vemurafenib
- 960 mg po bid (N=337)

Dacarbazine
- 1000 mg/m<sup>2</sup> iv q3w (N=338)
Waterfall Plots for BRAF$^{V600}$ Melanoma Patients Treated with Vemurafenib vs DTIC

48% confirmed response rate (2 complete responses)

5% confirmed response rate (0 complete responses)

BRAF inhibitors are better than chemotherapy for BRAF+ patients
Vemurafenib Improves Overall Survival in Previously Untreated Stage IV BRAF V600 Mutant Melanoma

Double oncogenic pathway inhibition to treat melanoma

\[ \text{BRAF}^{\text{V600}} \]

**Mutant melanoma**

- Improve ORR
- Prevent resistance (more durable responses and improved PFS)
- Improve OS

**Wild type normal cell**

- Decrease toxicities from paradoxical MAPK activation

Presented by: Antoni Ribas

Presented by Antoni Ribas at 2014 ASCO Annual Meeting
COMBI-d: Study Design

N = 947 screened

- BRAF V600E/K
- Unresectable stage III/IV
- Treatment naïve
- ECOG PS 0/1
- No brain mets, unless:
  - Treated
  - Stable ≥ 12 weeks

Stratification
- BRAF mut V600E v K
- LDH (>ULN v ≤ ULN)

Primary Endpoint: Investigator-assessed PFS
Secondary Endpoints: OS, overall response rate (ORR), duration of response, safety

Primary Analysis (PFS)
- [213 events]
- Aug 2013

Final Analysis (OS)
- [222 deaths]
- Jan 2015

Pre-planned interim OS
- [95 events]
COMBI-d: Overall Survival

Dabrafenib + Trametinib
Died: 99 (47%)
Med OS = 25.1 mo
(95% CI: 19.2-NR)

1-yr OS = 74%
2-yr OS 51%

Dabrafenib
Died: 123 (58%)
Median OS = 18.7 mo
(95% CI: 15.2-23.7)

HR 0.71 (95% CI: 0.55, 0.92)
P = 0.011

1-yr OS = 68%
2-yr OS 42%

Number at risk
Dabrafenib + trametinib 211 208 200 187 174 159 144 135 124 112 106 103 88 53 21 3 0 0
Dabrafenib + placebo 212 206 191 175 159 147 138 127 111 104 95 88 70 42 10 2 1 0

Dabrafenib+Trametinib med follow up 20 mo (range 0-30 mo); Dabrafenib med follow up 16 mo (range 0-32 mo).

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### COMBI-d: Treatment-Related Adverse Events (≥20% of Patients)

**Prepared by Georgina Long at 2015 ASCO Annual Meeting**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th><strong>Dabrafenib + Placebo</strong></th>
<th><strong>Dabrafenib + Trametinib</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades n (%)</td>
<td>Grade 3 n (%)</td>
</tr>
<tr>
<td>All Events</td>
<td>189 (90)</td>
<td>63 (30)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>52 (25)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Chills</td>
<td>29 (14)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>59 (28)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Rash</td>
<td>42 (20)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (15)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>49 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>70 (33)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>57 (27)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>55 (26)</td>
<td>0</td>
</tr>
</tbody>
</table>

*a Three grade 4 events; 1 grade 5 event, treatment-related (bile duct adenocarcinoma).

*b One grade 4 event; 5 fatal SAEs, not treatment related (3 intracranial hemorrhage, 1 pneumonia, 1 drowning).

*c Combined terms of palmar-plantar erythrodysesthesia and palmoplantar keratoderma.
Combination BRAF/MEK targeted therapy is better than BRAF alone
How should we sequence therapy in BRAF+ patients?
Antitumoral response: Targeted therapies vs. Immunotherapies (CTLA-4 antibodies)
Antitumoral response: Targeted therapies vs. Immunotherapies (CTLA-4 antibodies)
EA6134: Ipi/Nivo to D/T vs D/T to Ipi/Nivo

ECOG PS
1. 0
2. 1

LDH
1. Normal
2. Elevated

RANDOMIZE

Arm 1:
Ipi 3/Nivo 1 mg/kg/ q 3wks x 4 +Maint Nivo
PD
D 150 BID / T 2 mg Qd

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

ECOG and SWOG protocol – Atkins, Chmielowski
Anticipated opening 6/2015

Presented By Michael Atkins at 2015 ASCO Annual Meeting
2015 Approach to Metastatic Melanoma

Diagnosis of metastatic melanoma

BRAF mutation test

BRAF\textsuperscript{V600} mutation positive

- BRAF/MEK combo
- Ipilimumab
- Anti PD-1
- Combo anti CTLA4/anti PD-1
- Chemotherapy

BRAF\textsuperscript{V600} mutation negative

- Ipilimumab
- Anti PD-1
- Combo anti CTLA4/anti PD-1
- Chemotherapy
Summary & Conclusions

• Target the immune system or the MAP kinase pathway

• Immunotherapy
  – Ipilimumab beats vaccines & chemotherapy
  – Anti PD-1 beats chemotherapy after ipi
  – Anti PD-1 beats ipi
  – Combination ipi/anti PD-1 beats ipi and maybe anti PD-1

• Targeted therapy
  – BRAF beats chemotherapy
  – Combo BRAF/MEK beats BRAF

• How do we pick, how do we sequence in BRAF+ patients???