New Systemic Therapies in Advanced Melanoma

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Disclosures

• Equity interest:
  – Celldex, Targeted Therapeutics, Array, Incyte, Celgene, Pfizer, BioLine

• Honoraria:
  – Roche, AstraZeneca, Bristol-Myers, Celgene, Novartis, Merck
Minimization of Bias

• None of the material presented today has any relationship to the companies in which I hold an equity interest

• Only generic product names are used in this presentation, and the manufacturers will not be mentioned

• I have no authority over drug funding, and though I am on the BCCA PEC committee, I recuse myself from evaluations and discussions when there is even a remote possibility of bias
Targeted Therapies – BRAF and MEK Inhibition
BRAF and MEK Inhibitors: Mechanism of Action

- Provide concomitant inhibition of the pathway at the level of the RAF and MEK kinases, respectively.

- Synergistic in BRAF V600 mutation-positive melanoma cell lines and delayed the emergence of resistance in BRAF V600 mutation-positive melanoma xenografts compared with either inhibitor alone.

- Agents currently on the market are dabrafenib and vemurafenib (BRAF inhibitors), and trametinib and cobimetinib (MEK inhibitors).
# Response rates of BRAFi + MEKi

Consistent results across phase III trials

<table>
<thead>
<tr>
<th></th>
<th>COMBI-d (n=211) Cut off Jan 2015</th>
<th>COMBI-v (n=352) Cut off April, 2014</th>
<th>coBRIM (n=247) Cut off Jan 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>69 (61.8-74.8)</td>
<td>64 (59.1–69.4)</td>
<td>70 (63.5-75.3)</td>
</tr>
<tr>
<td><strong>CR, %</strong></td>
<td>16</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td><strong>PR, %</strong></td>
<td>53</td>
<td>51</td>
<td>54</td>
</tr>
<tr>
<td><strong>PD %</strong></td>
<td>6</td>
<td>6</td>
<td>~10</td>
</tr>
</tbody>
</table>

Immune Checkpoint Inhibitors – Anti-CTLA-4 and Anti-PD-1 Antibodies
Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies

CTLA-4 pathway blockade

PD-1 pathway blockade

CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.

### Immune Modulators – Objective Responses

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

*By RECIST v1.1. NR = not reached.
Agents Currently Available

• Anti-CTLA-4 antibodies
  – Ipilimumab

• Anti-PD-1 antibodies
  – Pembrolizumab
  – Nivolumab

• Combination therapy*
  – Ipilimumab + nivolumab
3-year Survival in Advanced Melanoma with BRAF and MEK Inhibition

**COMBI-d: PFS and OS**

- **Progression-Free Survival**
  - Dabrafenib + Trametinib (n = 211)
  - 2-y PFS, 30%
  - 3-y PFS, 22%
  - Dabrafenib + Placebo (n = 212)
  - 2-y PFS, 16%
  - 3-y PFS, 12%

- **Overall Survival**
  - Dabrafenib + Trametinib (n = 211)
  - 2-y OS, 52%
  - 3-y OS, 44%
  - Dabrafenib + Placebo (n = 212)
  - 2-y OS, 43%
  - 3-y OS, 32%

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

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*Presented at ASCO Annual Meeting '16*  
Presented by: Keith T. Flaherty, MD
Immune Modulators – Progression-Free Survival

Progression-Free Survival (Intent-to-Treat Population)

Median PFS, months (95% CI) | NIVO+IPI (N=314) | NIVO (N=516) | IPI (N=315)
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11.5 (6.9–16.7) | 6.3 (4.3–8.5) | 2.3 (2.0–3.4)

HR (95.0% CI) vs. IPI
- NIVO+IPI vs. IPI: 0.42 (0.31–0.57)*
- NIVO vs. IPI: 0.55 (0.43–0.76)*
- NIVO+IPI vs. NIVO: 0.76 (0.60–0.92)**

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

Number of patients at risk:
- Nivolumab + Ipilimumab: 314, 219, 174, 156, 133, 126, 103, 49, 8, 0
- Nivolumab: 316, 177, 146, 127, 114, 104, 54, 46, 8, 0
- Ipilimumab: 315, 137, 76, 58, 46, 40, 25, 15, 3, 0

Database lock Nov 2015
Nivolumab Shows Durable Survival in Heavily Pre-treated Patients

- Data from long-term follow-up of phase 1 study CA209-003
- 54% of patients had an immune-mediated AE (any grade) and 5% had a grade 3/4 event (gastrointestinal 2%, endocrine 2%, and hepatic 1%) \(^1,^2\)

AE, adverse event; NE, not evaluated.

Nivolumab Plus Ipilimumab in a Concurrent Regimen in Patients with Advanced Melanoma Showed 79-88% OS at 2 Years

- Data from a phase 1 trial (CA209-004) of nivolumab plus ipilimumab on a concurrent or sequenced regimen
- 62% of patients had grade 3/4 AEs on the concurrent regimen; there were no new safety signals and most events were manageable using standard protocols
- Historical 1-year survival rates with ipilimumab and nivolumab monotherapy in patients with advanced melanoma were 45.6% (phase 3) and 62% (phase 1), respectively

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Data from separate, noncomparative trials; use cross-trial comparisons with caution in the absence of data from a randomized, comparative trial.

Q3W, every 3 weeks.