2017 Master Class for Oncologists

Making the Most of New Therapeutic Approaches to Malignant Melanoma

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The Problem

- Incidence in US rising faster than any other cancer
- Approximately 60,000 new cases in US; 8,000 deaths
- Incidence varies by region
  - US: 15/100,000
  - New South Wales Australia: 1 in 20
Cytotoxic T-Lymphocyte Antigen-4: CTLA-4

T-cell activation
- T cell
- TCR
- CD28
- MHC
- APC
- CTLA4
- B7

T-cell inhibition
- T cell
- TCR
- CD28
- MHC
- APC
- CTLA4
- B7

T-cell potentiation
- T cell
- TCR
- CD28
- MHC
- APC
- CTLA4
- B7

Antibody binds CTLA-4

Wolchok et al., Ann NY Acad Sci, 2013
Ipilimumab: Clinical Experience

- Ipilimumab (MDX-010)
  - Fully Human Monoclonal IgG\textsubscript{1}

- Phase II ipilimumab monotherapy trials
  - 20-30\% durable disease control
  - Immune-related Adverse Events (irAEs); Events of Special Interest

- Generally manageable with vigilant follow-up and early steroids

O’Day et al. Ann Oncol 2010
Wolchok et al. Lancet Oncol 2010
Potential Side Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Any Grade</th>
<th>&gt;Grade3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis</td>
<td>40%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>30%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypophysitis/Thyroiditis</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Hepatitis and Pancreatitis</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>– Nephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Uveitis or Episcleritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Neuritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>70%</td>
<td>20%</td>
</tr>
<tr>
<td>IRAEs can be waxing and waning</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MDX010-20: Study Design

**Screening**
- Preiously treated
- HLA-A*0201 positive
- Pre-treated CNS metastases allowed

**Induction**
- **Ipilimumab** (3 mg/m2 IV q3wks X 4 doses) + **gp100**
- **Ipilimumab** (3 mg/m2 induction) + **placebo**
- **gp100 + placebo**

**Re-induction**
- **lpi + gp100**
- **lpi + placebo**
- **gp100 + placebo**

**Follow-up**
Survival Rate

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab + gp100</th>
<th>Ipilimumab alone</th>
<th>gp100 alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-yr</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>2-yr</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
</tr>
</tbody>
</table>

A Overall Survival

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>403</th>
<th>297</th>
<th>223</th>
<th>163</th>
<th>115</th>
<th>81</th>
<th>54</th>
<th>42</th>
<th>33</th>
<th>24</th>
<th>17</th>
<th>7</th>
<th>6</th>
<th>4</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab + gp100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab alone</td>
<td>137</td>
<td>106</td>
<td>79</td>
<td>56</td>
<td>38</td>
<td>30</td>
<td>24</td>
<td>18</td>
<td>13</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>gp100 alone</td>
<td>136</td>
<td>93</td>
<td>58</td>
<td>32</td>
<td>23</td>
<td>17</td>
<td>16</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Re-induction: Eligibility Criteria

Signs of clinical benefit

- Patients with progression after:
  - Stable disease of $\geq 6$ months duration (from baseline)
  - Confirmed objective response (PR or CR)

Acceptable safety

- No grade 3 irAEs
- No grade 4 toxicity
Time to Re-induction and Follow-up

BORR at induction

- Induction
- Re-induction: #1, #2, #3
- Ongoing
- Dead

Ipi+gp100

YEARS

1 2 3 5
Primary Analysis of Pooled OS Data: 1861 Patients

Median OS (95% CI): 11.4 (10.7–12.1)

3-year OS Rate (95% CI): 22% (20–24%)

Patients at Risk
Iplimumab 1861 839 370 254 192 170 120 26 15 5 0

Schadendorf et al. JCO 2015
Conclusions

• Ipilimumab is the first drug to demonstrate prolonged survival in a randomized trials in patients with metastatic melanoma

• Ipilimumab represents a new class of potent targeted T-cell stimulants

• Activity first/second line (following XRT, chemo, IL-2) and CNS disease

• Provides long-term survival benefit for a subset of patients

• Next generation immune checkpoint inhibitors (PD-1) developed
Role of PD-1 in Suppressing Antitumor Immunity

Role of PD-1 in Suppressing Antitumor Immunity

Changes in Target Lesions Over Time in Melanoma Patients

Dose administered IV Q2wk

Topalian et al. NEJM 2012
# Nivolumab Adverse Events

<table>
<thead>
<tr>
<th>Drug-Related Adverse Event</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tot Pop*</td>
<td>MEL</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>207 (70)</td>
<td>82 (79)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>72 (24)</td>
<td>30 (29)</td>
</tr>
<tr>
<td>Rash</td>
<td>36 (12)</td>
<td>21 (20)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33 (11)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>28 (9)</td>
<td>15 (14)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (8)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Appetite ↓</td>
<td>24 (8)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Hemoglobin ↓</td>
<td>19 (6)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (5)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

No. (%) of Patients, All Doses

AEs occurring in ≥5% of the total population.

†Common grade 3-4 AEs also included lymphopenia (3 pts) and abdominal pain and lipase increased (2 each). An additional 27 grade 3-4-related AEs were observed and one or more occurred in a single patient.

Topalian et al. NEJM 2012
Pembrolizumab (MK3475) is a Humanized IgG4, High-Affinity Anti-PD-1 Blocking Antibody

Approved in ipilimumab refractory, prior BRAFi population:
• 173 patients
• 2 mg/kg Q 3 weeks
• 24% response rate

Nivolumab in Previously Untreated Melanoma without BRAF Mutation

A Overall Survival

Patients Surviving (%)

No. at Risk
Nivolumab 210 185 150 105 45 8 0
Dacarbazine 208 177 123 82 22 3 0

B Progression-free Survival

Patients without Progression (%)

No. at Risk
Nivolumab 210 116 82 57 12 1 0
Dacarbazine 208 74 28 12 0 0 0

Hazard ratio for death, 0.42 (99.79% CI, 0.25–0.73)
P < 0.001

Patients Who Died
No./Total no.
Nivolumab 50/210
Dacarbazine 96/208

Median Survival
mo (95% CI)
Nivolumab Not reached
Dacarbazine 10.8 (9.3–12.1)

Patients Who Died or Had Disease Progression
No./Total no.
Nivolumab 108/210
Dacarbazine 163/208

Median Progression-free Survival
mo (95% CI)
Nivolumab 5.1 (3.5–10.8)
Dacarbazine 2.2 (2.1–2.4)

Hazard ratio for death or disease progression, 0.43 (95% CI, 0.34–0.56); P < 0.001
Nivolumab Overall Survival at 5 Years of Follow-up

- All Patients (events: 69/107), median and 95% CI: 17.3 (12.5–37.8)
- NIVO 3 mg/kg (events: 11/17), median and 95% CI: 20.3 (7.2–NR)

Number of Patients at Risk

<table>
<thead>
<tr>
<th>All Patients</th>
<th>NIVO 3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>107</td>
<td>17</td>
</tr>
<tr>
<td>86</td>
<td>15</td>
</tr>
<tr>
<td>64</td>
<td>11</td>
</tr>
<tr>
<td>51</td>
<td>9</td>
</tr>
<tr>
<td>49</td>
<td>8</td>
</tr>
<tr>
<td>49</td>
<td>7</td>
</tr>
<tr>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>29</td>
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<tr>
<td>17</td>
<td>6</td>
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<tr>
<td>15</td>
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<tr>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Hodi AACR 2016
## Phase I Study: Nivolumab + Ipilimumab

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Ipilimumab dose (mg/kg)</th>
<th>Nivolumab dose (mg/kg)</th>
<th>Concurrent regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
**Rapid and Durable Changes in Target Lesions**

1 mg/kg nivolumab + 3 mg/kg ipilimumab

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

At MTD 2 yr OS 88%

Wolchok et al. NEJM 2013
## Treatment-Related Select Adverse Events Occurring in ≥1 Patient

<table>
<thead>
<tr>
<th>Select Adverse Event</th>
<th>Concurrent Regimen All Cohorts (n=53)</th>
<th>Sequenced Regimen All Cohorts (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gr</td>
<td>Gr 3-4</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (6)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>7 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>3 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Skin</td>
<td>37 (70)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>20 (38)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>12 (23)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Lipase</td>
<td>10 (19)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Amylase</td>
<td>8 (15)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Presented by: Jedd D. Wolchok, MD, PhD
## Objective Response, Investigator-Assessed: Nivolumab + Ipilimumab vs. Ipilimumab

<table>
<thead>
<tr>
<th></th>
<th>All randomized patients (N = 142)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIVO + IPI (N = 95)</td>
<td>IPI (N = 47)</td>
<td></td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)a</strong></td>
<td>59 (48–69)</td>
<td>11 (4–23)</td>
<td></td>
</tr>
<tr>
<td><strong>P value for comparison</strong></td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Best overall response, %b</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>37</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>13</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Unable to determine</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

*a* (Complete response + partial response)/(all randomized patients); 95% CI is based on Clopper and Pearson method

*b* RECIST v1.1

CI = confidence interval
Nivolumab + Ipilimumab vs. Monotherapy

Progression-free Survival

**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

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

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)

N=475 N=476 N=951

Eggermont et al. Lancet Oncology 2015
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.

Eggermont et al. Lancet Oncology 2015
Overall Survival

No. of Deaths/Total No.  

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Deaths</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>162</td>
<td>475</td>
</tr>
<tr>
<td>Placebo</td>
<td>214</td>
<td>476</td>
</tr>
</tbody>
</table>

5-Yr Rate (95% CI) %

- Ipilimumab: 65.4 (60.8–69.6)
- Placebo: 54.4 (49.7–58.9)

Hazard ratio for death, 0.72 (95.1% CI, 0.58–0.88)
P = 0.001

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Year</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>475</td>
<td>431</td>
<td>369</td>
<td>325</td>
<td>290</td>
<td>199</td>
<td>62</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>476</td>
<td>413</td>
<td>348</td>
<td>297</td>
<td>273</td>
<td>178</td>
<td>58</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eggermont et al NEJM 2016
Treatment options for patients with Stage III melanoma

• Observation
• IFN
• Participation in a clinical trial
• Ipiluminab (antiCTLA4) clinical trials
  – EORTC Ipilimumab vs. observation
  – ECOG study Ipilimumab vs. high dose IFN
• Anti-PD-1 adjuvant trials being conducted
### Management of Inflammatory Adverse Events

#### Algorithms

- **Diarrhea/Colitis**
  - High grade/prolonged low grade
  - Rule out other causes/endoscopy, IV steroids, slow taper (e.g. 1 month), infliximab for refractory cases

- **Hepatitis**: Follow LFTs, pancreatic enzymes
  - High grade: steroids, mycophenylate

- **Pneumonitis**
  - Asymptomatic infiltrate vs. symptom (cough, SOB)
  - Rule out other causes (e.g. flu); hold drug vs. steroids, infliximab resistant cases

- **Endocrinopathies** – clinical suspicion, pituitary and thyroid
Conclusions

• Blockade of the PD-1 pathway represents a new immune therapy for patients with melanoma

• Preliminary data correlating PD-L1 expression in pretreatment tumor biopsies with clinical outcomes will be further explored

• Pembrolizumab and Nivolumab are approved following ipilimumab and BRAF targeted therapy if BRAF mutation; NCCN first-line

• Nivolumab+ Ipilimumab approval

• PD-1 based treatment considered front-line therapy

• Algorithms for management of inflammatory adverse events

• Further combinations under development
Downstream signaling events: The MAPK pathway

- Plasma membrane
- Ras
- Raf
- MEK
- Erk
- Proliferation

RAS mutations: 15% cancers, 90% pancreas (farnesyl transferase inhibitors)
BRAF mutations: 66% malignant melanomas (Davies and Futreal, Nature 2002)
Selective BRAFi
Vemurafenib

PET and CT Responses

Flaherty et al. NEJM 2010
Phase III BRIM3 Study design

**Screening**
- BRAF\(^{V600E}\) mutation

**Stratification**
- Stage
- ECOG PS (0 vs 1)
- LDH level (↑ vs nl)
- Geographic region
- No active CNS disease

**Randomization**
- N=675

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

**Dacarbazine**
- 1000 mg/m\(^2\) iv q3w (N=338)

Chapman NEJM 2011
Overall Survival

Vemurafenib (N=336)
Est 6 mo survival 84%

Dacarbazine (N=336)
Est 6 mo survival 64%

Hazard ratio 0.37
(95% CI; 0.26 - 0.55)
Log-rank P<0.0001

No. of patients in follow up
Dacarbazine: 336 283 192 137 98 64 39 20 9 1 1
Vemurafenib: 336 320 266 210 162 111 80 35 14 6 1
Progression-free Survival

Hazard Ratio 0.26
(95% CI; 0.20 - 0.33)
Log-rank P<0.0001

Progression-free survival (%)

Months

Dacarbazine (N=274)

Vemurafenib (N=275)

Median 1.6 mos | Median 5.3 mos

No. of patients in follow up

Dacarbazine 274 213 85 48 28 16 10 6 3 0

Vemurafenib 275 268 211 122 105 50 35 16 4 3
Conclusions

- Selective BRAF inhibitors are a breakthrough for melanoma

- Vemurafenib associated with 63% decrease in hazard of death \( (p<.0001) \)

- 74% decrease in hazard of tumor progression \( (p<.0001) \)

- Benefit seen in all subgroups and baseline characteristics

- Despite a 50-80% response rate, vast majority of patients recur and develop resistance
BRAFi Mechanisms of Resistance

Luke and Hodi, The Oncologist
BRAFi + MEKi: Overall Survival Improved Dabrafenib (BRAFi) + Trametinib (MEKi)

Overall Survival

- Increased incidence of pyrexia
- Decreased incidence of skin manifestations of BRAFi

Vemurafenib (BRAFi) + Cobimetinib (MEKi) Improves Survival


<table>
<thead>
<tr>
<th>Months</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
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<tr>
<td>1</td>
<td>90</td>
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<tr>
<td>2</td>
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<td>3</td>
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<td>20</td>
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<td>9</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.65 (95% CI, 0.42–1.00)  
P = 0.046

<table>
<thead>
<tr>
<th>Patients Who Died</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib + cobimetinib</td>
<td>34</td>
</tr>
<tr>
<td>Vemurafenib + placebo</td>
<td>51</td>
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<table>
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<th>No. at Risk</th>
<th>Months</th>
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<tbody>
<tr>
<td>Vemurafenib + cobimetinib</td>
<td>243 229 182 112 62 20 6</td>
</tr>
<tr>
<td>Vemurafenib + placebo</td>
<td>245 227 166 101 53 21 2</td>
</tr>
</tbody>
</table>
BRAF Targeted Therapy

- Side effects: rash, arthritis, diarrhea, squamous cell skin cancer, keratoacanthoma, photosensitivity, LFTs, prolonged QTc

- FDA approved for unresectable or stage IV melanoma with BRAF V600E (Vemurafenib, Dabrafenib + Trametinib)

- Not indicated for wild type BRAF

- Secondary skin cancers: paradoxical activation of MAPK in HRAS mutated keratinocytes

- Pyrexia and less skin toxicity with BRAFi + MEKi combination
What to do for a patient with BRAF mutated melanoma?

- Immune Therapy vs. Targeted Therapy
  - PD-1 based therapy front-line regardless of BRAF status
- Immune combo vs. PD-1 alone
  - Efficacy weighed with potential side effects
  - Biomarker: PD-L1 expression?
- After PD-1 based therapy
  - Targeted therapy vs Ipilimumab alone (if not get previously)
- Clinical trials/further data maturation to guide
Melanoma Treatment Advances

Future is Fast Paced

- Immune modulation
  - CTLA-4 Blockade
  - PD-1 Blockade
  - CTLA-4 + PD-1 Blockades
  - PD-1 based therapy front-line
  - Ipilimumab considered following PD-1
- Improved genetic understanding
  - BRAFi
  - MEKi
  - BRAFi + MEKi
- Sequencing: Immune Therapy vs. Targeted Therapy
- Combinatorial Approaches
Disclosures and Questions

• Advisor
  – Novartis, Merck

• Non-paid Advisor and/or Research Support
  – Bristol-Myers Squibb, Genentech

• Questions: stephen_hodi@dfci.harvard.edu