Immunotherapy of Melanoma

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Overview

- Metastatic Melanoma
- Adjuvant therapy for High-risk
- Practical Questions
- Future Directions
Overview

• Metastatic Melanoma
• Adjuvant therapy for High-risk
• Practical Questions
• Future Directions
Today’s Immunotherapy = Checkpoint Inhibitors
Check-Point Inhibitors Approved for Melanoma

- Anti CTLA4 antibody: Ipilimumab
- Anti PD-1 inhibitors: 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

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\(^b\)
- 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
- 10 mg/kg IV Q3W

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

**Key End Points**
- 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><strong>ORR, % (95% CI)</strong></td>
<td>42 (38-46)</td>
<td>16 (12-21)</td>
</tr>
<tr>
<td><strong>Best overall response, % (95% CI)</strong></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>
Overall Survival
Median Follow-Up 45.9 (0.3–50.0) Months

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th></th>
<th>Treatment-Naive Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events, n</td>
<td>HR* (95% CI)</td>
<td>Median,* mo (95% CI)</td>
<td>Events, n</td>
</tr>
<tr>
<td>Pembro</td>
<td>309</td>
<td>0.73 (0.61–0.89)</td>
<td>32.7 (24.5–41.6)</td>
<td>193</td>
</tr>
<tr>
<td>Ipi</td>
<td>164</td>
<td></td>
<td>15.9 (13.3–22.0)</td>
<td>104</td>
</tr>
</tbody>
</table>

*Based on Cox regression model with treatment as covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative), and ECOG (0 vs 1); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum was excluded from treatment comparison. *Derived by the product-limit (Kaplan-Meier) method for censored data. Data cutoff: Dec 4, 2017.
Blocking CTLA-4 and PD-1

Early immune response: T cell activation

Blood vessel

Peripheral tissues

Tumor cells

Lymph node

Effector Phase

APC

T Cell

MHC

TCR

1st signal

2nd signal

B7

CD28

INHIBITION

ACTIVATION

Ipilimumab and Tremelimumab

Nivolumab

Pembrolizumab

Pidilizumab

Atezolizumab

Durvalumab

Avelumab
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

N=315

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

Treat until progression** or unacceptable toxicity

*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.

Presented By Jedd Wolchok at 2015 ASCO Annual Meeting
### 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.
CM-67 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>11.5 (8.7–19.3)</td>
<td>6.9 (5.1–9.7)</td>
<td>2.9 (2.8–3.2)</td>
</tr>
<tr>
<td>HR (95% CI) vs. IPI</td>
<td>0.43 (0.35–0.52)</td>
<td>0.55 (0.45–0.66)</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.78 (0.64–0.96)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Database lock May 24, 2017

Wolchok, NEJM, 2017
CM-67 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>Median OS, months (95% CI)</td>
<td>38.2-NR</td>
<td>37.6 (29.1-NR)</td>
<td>19.9 (16.9-24.6)</td>
</tr>
<tr>
<td>HR (99.5% CI) vs. IPI</td>
<td>0.55 (0.45–0.69)*</td>
<td>0.65 (0.53–0.80)*</td>
<td>-</td>
</tr>
<tr>
<td>HR (99.5% CI) vs. NIVO</td>
<td>0.85 (0.68–1.07)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Database lock May 24, 2017

Wolchok, NEJM, 2017
Decision Point….

Immunotherapy

- PD-1 alone
- PD-1/CTLA-4 Combination
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>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
<td>Grade 3-4</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

\(^a\)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).

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

- Skin (n=18): 5.6 (0.1 – 55.0)
- Skin (n=5): 19.4 (1.3 – 50.9)
- Gastrointestinal (n=46): 7.4 (1.0 – 48.9)
- Gastrointestinal (n=7): 26.3 (13.1 – 57.0)
- Pulmonary (n=3): 11.3 (3.3 – 23.7)
- Pulmonary (n=1): 50.9 (50.9 – 50.9)
- Renal (n=6): 6.7 (6.7 – 6.7)
- Renal (n=1): 11.3 (3.3 – 23.7)

Circles represent medians; bars signify ranges

Toxicity Earlier
Longer Time to Resolution

Larkin J et al ECC 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 (13.0–18.6)</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>

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

### 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 65.2% for NIVO+IPI and 55.0% for NIVO
Overview

• Metastatic Melanoma
• Adjuvant therapy for High-risk
• Practical Questions
• Future Directions
**EORTC 18071: phase 3 study design**

**Key eligibility criteria**
- Stage IIIA, IIB, or IIC melanoma metastatic to lymph node
- Complete and adequate resection of stage III melanoma
- No prior systemic therapy

**Stratified by:**
- Stage (IIIA vs IIB vs IIC 1-3 positive lymph nodes vs IIC ≥ 4 positive lymph nodes)
- Region of the world

**Randomized, double-blind, phase 3 study**

**INDUCTION**
- Ipilimumab 10 mg/kg
  - Q3W × 4 (n = 475)
- Placebo
  - Q3W × 4 (n = 476)

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

**Primary endpoint**
- RFS

**Secondary endpoints**
- OS, DMFS, safety, HRQOL

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

**DMFS, distant metastasis-free survival; HRQOL, health-related quality of life; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q12W, every 12 weeks; RFS, relapse-free survival.**

EORTC 18071
Ipilimumab vs Placebo
Safety Summary

**RFS (per IRC)**

<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>0.75 (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>

*Stratified by stage provided at random. CI = confidence interval.

**OS**

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths/patients</td>
<td>152/475</td>
<td>214/476</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.72 (0.53, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Stratified by stage provided at random.

**Table: Ipilimumab (n = 471)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<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 leading to 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>

**Deaths due to drug-related AEs**
- 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

Eggermont et al. NEJM 2016
CheckMate 238: Study Design

Patients with:

• High-risk, completely resected stage IIIB/IIIC or stage IV (AJCC 7th edition) melanoma
• No prior systemic therapy
• ECOG 0-1

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

1:1

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

Follow-up
Maximum treatment duration of 1 year
n = 453
n = 453

Jeffrey Weber, Oral Presentation ASCO 2018
Primary Endpoint: RFS in All Patients

<table>
<thead>
<tr>
<th>Months</th>
<th>Number of patients at risk (NIVO)</th>
<th>Number of patients at risk (IPI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>453</td>
<td>453</td>
</tr>
<tr>
<td>1</td>
<td>394</td>
<td>314</td>
</tr>
<tr>
<td>2</td>
<td>353</td>
<td>270</td>
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<tr>
<td>3</td>
<td>331</td>
<td>251</td>
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<td>4</td>
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<td>5</td>
<td>291</td>
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<td>6</td>
<td>280</td>
<td>204</td>
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<td>7</td>
<td>264</td>
<td>205</td>
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<tr>
<td>8</td>
<td>283</td>
<td>28</td>
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<tr>
<td>9</td>
<td>291</td>
<td>23</td>
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<tr>
<td>10</td>
<td>264</td>
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<td>11</td>
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<td>12</td>
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<td>264</td>
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<td>14</td>
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<td>16</td>
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<td>15</td>
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<td>15</td>
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<tr>
<td>16</td>
<td>264</td>
<td>14</td>
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<td>17</td>
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<td>18</td>
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<td>283</td>
<td>0</td>
</tr>
<tr>
<td>33</td>
<td>291</td>
<td>0</td>
</tr>
</tbody>
</table>

**Events/patients**
- NIVO: 171/453
- IPI: 221/453

**Median (95% CI)**
- NIVO: 30.8 (30.8, NR)*
- IPI: 24.1 (16.6, NR)

**HR (95% CI)**
- 0.66 (0.54, 0.81)

**Log-rank P value**
- <0.0001

*Median estimate not reliable or stable due to few patients at risk.

Jeffrey Weber, Oral Presentation ASCO 2018
<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>Any AE</td>
<td>438 (97)</td>
<td>115 (25)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>385 (85)</td>
<td>65 (14)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation</td>
<td>44 (10)</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>35 (8)</td>
<td>16 (4)</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

Weber, J et al ESMO 2017
EORTC 1325/KEYNOTE-54: Study Design

High-risk, resected, stage III cutaneous melanoma

N=1019

Randomized 1:1

PART 1: ADJUVANT THERAPY

Pembrolizumab 200 mg IV Q3W 1 year

Placebo IV Q3W 1 year

Total of 18 doses

Recurrence >6 months

Recurrence

Cross-over

PART 2: POST RECURRENCE

Pembrolizumab 200 mg IV Q3W until progression or recurrence, up to 2 years

Stratification factors:

✓ Stage: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes
✓ Region: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

• RFS (per investigator) in overall population, and RFS in patients with PD-L1-positive tumors

Secondary Endpoints:

• DMFS and OS in all patients, and in patients with PD-L1-positive tumors; Safety, Health-related quality of life

UNBLINDING/cross-over: Anti-PD1 for all or just as good if only for those at time of recurrence?
Recurrence-Free Survival in the ITT Population

Primary endpoint

% alive and recurrence-free

Treatment arm | Total | Event | HR (98.4% CI)
--- | --- | --- | ---
Pembrolizumab | 514 | 135 | 0.57 (0.43-0.74)
Placebo | 505 | 216 | Reference

Stratified Logrank P-value: <.0001

Patients at risk

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<th>Months</th>
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*Stratified by stage given at randomization

HR 0.57
Interferon
Overview

• Metastatic Melanoma
• Adjuvant therapy for High-risk
• Practical Questions
• Future Directions
Practical Questions

• What is the correct duration?
  – Are responses durable after stopping treatment?

• What is the correct first choice for BRAF+ patients?
Disposition of Patients Completing ≥94 Weeks of Pembrolizumab Treatment

556 patients received pembrolizumab

103 (18.5%) completed 2 year pembrolizumab treatment

- Median follow-up after ≥94 weeks pembro: 20.3 (0.03-24.8) mo

- 28 (27.2%) CR
  - 26 patients had an ongoing response
  - 2 (7.1%) confirmed PDa
  - 3 received 2nd course of pembrolizumabb

- 65 (63.1%) PR
  - 56 patients had an ongoing response
  - 9 (13.8%) confirmed PDa
  - 4 received 2nd course of pembrolizumab

- 10 (9.7%) SD
  - 7 patient had an ongoing SD
  - 3 (30%) confirmed PDa
  - 1 received 2nd course of pembrolizumab

*aConfirmed PD by investigator per irRC (confirmatory scan or no subsequent scan or not evaluable). An additional 5 pts with unconfirmed progressive disease were observed. bIncludes 1 patient who discontinued early with CR and then progressed. Data cutoff: Dec 4, 2017.
PFS\textsuperscript{a} in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 103)

\textsuperscript{a}Per immune-related response criteria by investigator review; time is measured from last dose of pembrolizumab. Data cutoff: Dec 4, 2017.
Duration of Response in Patients With ≥94 Weeks of Pembrolizumab\(^a\) (n = 103)

- 89\(^c\) (86%) patients who completed 2 years on pembrolizumab were progression-free at 20 months after end of therapy

\(^a\)With SD, CR, or PR. \(^b\)Length of each bar represents time to the last scan. \(^c\)An additional 5 patients have unconfirmed progression. Data cutoff: Dec 4, 2017.
Practical Questions

• What is the correct duration?
  – Are responses durable after stopping treatment?

• What is the correct first choice for BRAF+ patients?
### 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\(^4,5,6\)

---

Decision Point….

BRAF mutation test

BRAF\textsuperscript{V600} mutation negative

Immunotherapy

BRAF\textsuperscript{V600} mutation positive

Immunotherapy

Or

MAP-K Targeted Therapy
KEYNOTE-001: Phase I RECIST Response (v1.1)

Total population n=581
- ORR 33%
- CR 8%

Median Change: -36%

IPI-T 71%
IPI-N 71%

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
<table>
<thead>
<tr>
<th>Phase</th>
<th>Vemurafenib(^1)</th>
<th>Dabrafenib(^2)</th>
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<tr>
<td>Phase 1</td>
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<td>Phase 2</td>
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<td>Phase 3</td>
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Antitumoral response: Targeted therapies vs. Immunotherapies (CTLA-4 antibodies)
Contemplating the Options

Anti-PD1 therapy  
BRAF-targeted therapy

**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 q 2wks x 42

Dabrafenib 150mg po BID  
Trametinib 2 mg daily

**Arm B:**
Dabrafenib 150mg po BID  
Trametinib 2 mg daily

**PD**

ECOG PS  
0  
1  
Serum LDH

RANDOMIZE
Overview

• Metastatic Melanoma
• Adjuvant therapy for High-risk
• Practical Questions
• Future Directions
The T Cell-Inflamed Tumor Microenvironment is Characterized by Expression of Immune-Inhibitory Pathways and Predicts Outcomes to Immunotherapy

CD8
FoxP3
PD-L1
IDO

Ribas et al. J Clin Oncol 33, 2015 (suppl; abstr 3001)
Combining Immunotherapy and Targeted Therapy for Melanoma?

**Improved Survival With Ipilimumab in Patients with Metastatic Melanoma**


**Improved Survival With Vemurafenib in Melanoma With BRAF V600E Mutation**


Targeted-Immuno Triplets: BRAF + MEK + PD1/L1

Multiple Triplet Combinations Launching Into Phase III:

- Dabrafenib + Trametinib + Pembrolizumab
- Dabrafenib + Trametinib + PDR-001
- Vemurafenib + Cobimetinib + Atezolizumab
IDO Inhibitors: Background

• Upregulation of IDO1 is a potential mechanism to evade immunosurveillance
  – ↓ Tryptophan  ↑ Kynurenine
  – ↓ T_{eff} and NK cells
  – ↑ T_{reg} cells, MDSCs, TAMs
• Epacadostat: IDO1 enzyme inhibitor
• Pembrolizumab: anti-PD-1 humanized antibody
Phase I/II Combination Epacadostat + Pembrolizumab

**ECHO-202 / KEYNOTE-037**
- Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
  - MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID
- Phase 1/2 efficacy in treatment-naive melanoma:
  - ORR = 55%
  - Median PFS = 22.8 mo (12.4 mo all melanoma)

**Graph:**
- Treatment-Naive Melanoma Phase 1/2 (n=54)
  - ORR = 55%

**Legend:**
- Epacadostat 100 mg BID + Pembrolizumab 200 mg Q3W
- Other Epacadostat doses + Pembrolizumab 200 mg Q3W

---

BID, twice daily; MTD, maximally tolerated dose; PD-L1, programmed death ligand-1; Q3W, every 3 weeks.
Phase III Randomized Placebo Controlled Trial

Key Eligibility Criteria

- Unresectable stage III or IV melanoma, advanced/metastatic disease
  - Patients with BRAF mutation could have received prior BRAF/MEK therapy
  - Prior anti-CTLA-4 or interferon in adjuvant setting permitted
- ECOG performance status 0–1
- No active CNS metastases

Stratification

- PD-L1 status (positive \(^a\) vs negative)
- BRAF mutation status
  - Wild type
  - Mutant with prior BRAF-directed therapy
  - Mutant without prior BRAF-directed therapy

Epacadostat 100 mg PO BID + Pembrolizumab 200 mg IV Q3W
n=354

Placebo + Pembrolizumab 200 mg IV Q3W
n=352

N=706 R 1:1

- Primary endpoints: PFS (RECIST v1.1) and OS
- Secondary endpoints: ORR (RECIST v1.1), DOR, safety

BID, twice daily; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

\(^a\): \(\geq 1\%\) staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).

Georgina V. Long
Progression-Free Survival

- **Events, n (%)**
  - **E + P**: 218 (61.6) 4.7 (2.9–6.8)
  - **Placebo + P**: 219 (62.2) 4.9 (2.9–6.8)

- **HR (95% CI)**: 1.00 (0.83–1.21)
  - **P = 0.517**

**Number at risk**

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**BICR**, blinded independent central review; CI, confidence interval; E, epacadostat; HR, hazard ratio; P, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors. PFS defined as time from randomization to disease progression or death, whichever occurred first.
Summary & Conclusions

- Immunotherapy with checkpoint inhibitors is standard of care for most patients
  - Single agent PD1
  - Combination PD-1/CTLA-4
- For BRAF+ patients the choice is based on clinical judgment
- It has recently been approved for adjuvant therapy
- Future therapies will address better combinations and overcoming resistance
How I Treat Metastatic Melanoma

Diagnosis of metastatic melanoma

BRAF mutation test

BRAF\text{V}^{600} mutation positive

BRAF/MEK combo
- Anti PD-1
- Combo antiCTLA4/anti PD-1
- Ipilimumab

BRAF\text{V}^{600} mutation negative

Anti PD-1
- Combo antiCTLA4/antiPD-1
- Ipilimumab
How I treat High Risk Melanoma Adjuvant Therapy

Sentinel Node Biopsy Positive
BRAF mutation test

BRAF\textsuperscript{V600} mutation negative

Anti- PD1

BRAF\textsuperscript{V600} mutation positive

Anti- PD1
Or
Dabrafenib + Trametinib
Clinical Trials!