Melanoma

Andrew Haydon
Alfred Hospital
Historical Perspective
BSC

Cochrane Database Systematic Review 2000
Systemic treatments for metastatic melanoma

Objective
To review the benefits of systemic therapy compared to BSC/placebo in metastatic melanoma

Results
“No randomized controlled trials were found comparing a systemic therapy with placebo or BSC in metastatic cutaneous melanoma”

Crosby T, Fish R, Coles B, Mason M. 2000
DTIC vs. Temozolomide

305 pts with measurable metastatic melanoma
Randomized to receive
  TMZ 200mg/M2/Day for 5/7 q28/7
  DTIC 250mg/M2/Day for 5/7 q21/7
Primary end point was OS
CNS disease was excluded
PS 0-2
Treatments were very well tolerated

Fig 2. PFS in the temozolomide (thick line) and DTIC (thin line) treatment groups

1.9 \( \pm \) 1.5 months

\( P=0.012 \)
Fig 1. Overall survival in the temozolomide (thick line) and DTIC (thin line) treatment groups.

7.7 vs. 6.4 months

P=0.20
DTIC vs. Fotemustine

229 pts with measurable metastatic melanoma
Randomized
   Fotemustine 100mg/M2 Day 1, 8, 15
   DTIC 250mg/M2/Day for 5/7 q28/7
Primary end point was response rate
CNS disease was allowed
PS 0-1

Fig 1. Kaplan-Meier plot of time to disease progression (months) in the full analysis set

1.8 vs. 1.9 months

P=0.14
Fig 3. Kaplan-Meier plot of overall survival in the randomized set

- Fotemustine (n = 112)
- Dacarbazine (n = 117)

7.3 vs. 5.6 months

P = 0.07
Adjuvant Treatment
**Adjuvant Interferon (DFS)**

Review: Interferon alpha for the adjuvant treatment of cutaneous melanoma
Comparison: 1 Interferon alpha versus any other comparator
Outcome: 1 Disease-free survival (DFS)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio IV,Fixed,95% CI</th>
<th>Weight</th>
<th>Hazard Ratio IV,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwala 2011</td>
<td>-0.09 (0.08)</td>
<td></td>
<td>12.8%</td>
<td>0.91 [0.78, 1.07]</td>
</tr>
<tr>
<td>Cameron 2001</td>
<td>-0.228 (0.221)</td>
<td></td>
<td>1.7%</td>
<td>0.80 [0.52, 1.23]</td>
</tr>
<tr>
<td>Cascinelli 2001</td>
<td>-0.133 (0.195)</td>
<td></td>
<td>2.2%</td>
<td>0.88 [0.60, 1.28]</td>
</tr>
<tr>
<td>Creagan 1995</td>
<td>-0.274 (0.158)</td>
<td></td>
<td>3.3%</td>
<td>0.76 [0.56, 1.04]</td>
</tr>
<tr>
<td>Eggermont 2005</td>
<td>-0.128 (0.08)</td>
<td></td>
<td>12.8%</td>
<td>0.88 [0.75, 1.03]</td>
</tr>
<tr>
<td>Eggermont 2008</td>
<td>-0.175 (0.075)</td>
<td></td>
<td>14.6%</td>
<td>0.84 [0.72, 0.97]</td>
</tr>
<tr>
<td>Garbe 2008</td>
<td>-0.371 (0.156)</td>
<td></td>
<td>3.4%</td>
<td>0.69 [0.51, 0.94]</td>
</tr>
<tr>
<td>Grob 1998</td>
<td>-0.301 (0.143)</td>
<td></td>
<td>4.0%</td>
<td>0.74 [0.56, 0.98]</td>
</tr>
<tr>
<td>Hancock 2004</td>
<td>-0.094 (0.098)</td>
<td></td>
<td>8.5%</td>
<td>0.91 [0.75, 1.10]</td>
</tr>
<tr>
<td>Hansson 2011</td>
<td>-0.223 (0.091)</td>
<td></td>
<td>9.9%</td>
<td>0.80 [0.67, 0.96]</td>
</tr>
<tr>
<td>Kirkwood 1996</td>
<td>-0.407 (0.144)</td>
<td></td>
<td>4.0%</td>
<td>0.67 [0.50, 0.88]</td>
</tr>
<tr>
<td>Kirkwood 2000</td>
<td>-0.211 (0.111)</td>
<td></td>
<td>6.7%</td>
<td>0.81 [0.65, 1.01]</td>
</tr>
<tr>
<td>Kirkwood 2001</td>
<td>-0.399 (0.118)</td>
<td></td>
<td>5.9%</td>
<td>0.67 [0.53, 0.85]</td>
</tr>
<tr>
<td>Kirkwood 2001a</td>
<td>-0.528 (0.306)</td>
<td></td>
<td>0.9%</td>
<td>0.59 [0.32, 1.07]</td>
</tr>
<tr>
<td>Kleeberg 2004</td>
<td>0.049 (0.111)</td>
<td></td>
<td>6.7%</td>
<td>1.05 [0.84, 1.31]</td>
</tr>
<tr>
<td>McMaster 2008</td>
<td>-0.198 (0.278)</td>
<td></td>
<td>1.1%</td>
<td>0.82 [0.48, 1.41]</td>
</tr>
<tr>
<td>Pehamberger 1998</td>
<td>-0.491 (0.211)</td>
<td></td>
<td>1.8%</td>
<td>0.61 [0.40, 0.93]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**
Heterogeneity: Chi² = 18.98, df = 16 (P = 0.27); I² = 16%
Test for overall effect: Z = 6.63 (P < 0.00001)
Test for subgroup differences: Not applicable
Adjuvant Interferon (O.S.)

Review: Interferon alpha for the adjuvant treatment of cutaneous melanoma
Comparison: 1 Interferon alpha versus any other comparator
Outcome: 2 Overall Survival (OS)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio IV,Fixed,95% CI</th>
<th>Weight</th>
<th>Hazard Ratio IV,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwala 2011</td>
<td>0.01 (0.11)</td>
<td></td>
<td>8.9 %</td>
<td>1.01 [0.81, 1.25]</td>
</tr>
<tr>
<td>Cameron 2001</td>
<td>-0.151 (0.231)</td>
<td></td>
<td>2.0 %</td>
<td>0.86 [0.55, 1.35]</td>
</tr>
<tr>
<td>Cascinelli 2001</td>
<td>-0.051 (0.117)</td>
<td></td>
<td>7.9 %</td>
<td>0.95 [0.76, 1.20]</td>
</tr>
<tr>
<td>Creagan 1995</td>
<td>-0.105 (0.171)</td>
<td></td>
<td>3.7 %</td>
<td>0.90 [0.64, 1.26]</td>
</tr>
<tr>
<td>Eggermont 2005</td>
<td>-0.094 (0.089)</td>
<td></td>
<td>13.6 %</td>
<td>0.91 [0.76, 1.08]</td>
</tr>
<tr>
<td>Eggermont 2008</td>
<td>0.001 (0.09)</td>
<td></td>
<td>13.3 %</td>
<td>1.00 [0.84, 1.19]</td>
</tr>
<tr>
<td>Garbe 2008</td>
<td>-0.478 (0.171)</td>
<td></td>
<td>3.7 %</td>
<td>0.62 [0.44, 0.87]</td>
</tr>
<tr>
<td>Grob 1998</td>
<td>-0.357 (0.172)</td>
<td></td>
<td>3.6 %</td>
<td>0.70 [0.50, 0.98]</td>
</tr>
<tr>
<td>Hancock 2004</td>
<td>-0.062 (0.116)</td>
<td></td>
<td>8.0 %</td>
<td>0.94 [0.75, 1.18]</td>
</tr>
<tr>
<td>Hansson 2011</td>
<td>-0.094 (0.103)</td>
<td></td>
<td>10.2 %</td>
<td>0.91 [0.74, 1.11]</td>
</tr>
<tr>
<td>Kirkwood 1996</td>
<td>-0.315 (0.154)</td>
<td></td>
<td>4.5 %</td>
<td>0.73 [0.54, 0.99]</td>
</tr>
<tr>
<td>Kirkwood 2000</td>
<td>-0.021 (0.122)</td>
<td></td>
<td>7.2 %</td>
<td>0.98 [0.77, 1.24]</td>
</tr>
<tr>
<td>Kirkwood 2001</td>
<td>-0.328 (0.162)</td>
<td></td>
<td>4.1 %</td>
<td>0.72 [0.52, 0.99]</td>
</tr>
<tr>
<td>Kleeberg 2004</td>
<td>-0.021 (0.12)</td>
<td></td>
<td>7.5 %</td>
<td>0.98 [0.77, 1.24]</td>
</tr>
<tr>
<td>McMasters 2008</td>
<td>0.068 (0.256)</td>
<td></td>
<td>1.6 %</td>
<td>1.07 [0.65, 1.77]</td>
</tr>
</tbody>
</table>

Total (95% CI)
Heterogeneity: Chi² = 14.93, df = 14 (P = 0.38); I² = 6%
Test for overall effect: Z = 2.97 (P = 0.0029)
Test for subgroup differences: Not applicable
EORTC 18952 and EORTC 18991

2C Survival

No ulceration: HR 1.11 (99% CI 0.86–1.41), p=0.20.
Ulceration: HR 0.72 (99% CI 0.55–0.93), p=0.001.
IPILIMUMAB VS PLACEBO AFTER COMPLETE RESECTION OF STAGE III MELANOMA: FINAL OVERALL SURVIVAL RESULTS FROM THE EORTC 18071 RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

Alexander MM Eggermont, 1 Vanna Chiarion Sileni, 2 Jean-Jacques Grob, 3 Reinhard Dummer, 4 Jedd D Wolchok, 5 Henrik Schmidt, 6 Omid Hamid, 7 Caroline Robert, 1 Paolo A Ascierto, 8 Jon M Richards, 9 Céleste Lebbé, 10 Virginia Ferraresi, 11 Michael Smylie, 12 Jeffrey S Weber, 13, * Corina Taitt, 14 Veerle de Pril, 14 Gaetan de Schaetzen, 15 Stefan Suciu, 15 Alessandro Testori 16

1 Gustave Roussy Cancer Campus Grand Paris, Villejuif, France; 2 Oncology Institute of Veneto–Istituto di Ricovery e Cura a Carattere Scientifico, Padua, Italy; 3 Aix-Marseille University, Hôpital de La Timone, Marseille, France; 4 University of Zürich Hospital, Zürich, Switzerland; 5 Memorial Sloan Kettering Cancer Center, New York, NY, USA; 6 Aarhus University Hospital, Aarhus, Denmark; 7 The Angeles Clinic and Research Institute, Los Angeles, CA, USA; 8 Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; 9 Oncology Specialists S.C., Park Ridge, IL, USA; 10 Department of Dermatology and Centred Investigation Clinique, U-976 Hôpital Saint Louis, Université Paris Diderot, Paris, France; 11 Istituti Fisioterapici Ospitalieri, Rome, Italy; 12 Cross Cancer Institute, Edmonton, Alberta, Canada; 13 H Lee Moffitt Cancer Center, Tampa, FL, USA; 14 Bristol-Myers Squibb, Princeton, NJ, USA; 15 EORTC Headquarters, Brussels, Belgium; 16 European Institute of Oncology, Milan, Italy. *Current affiliation: Perlmutter Cancer Center at NYU-Langone Medical Center, New York, NY, USA

Abstract Number LBA 3070
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

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)

Enrollment Period: June 2008 to July 2011

Q3W = every 3 weeks; Q12W = every 12 weeks; R = randomization.
Study Endpoints

- **Primary endpoint**
  - RFS by independent review committee (IRC)

- **Secondary endpoints**
  - OS, distant metastasis-free survival (DMFS), safety profile, health-related quality of life

- **Current analysis** (minimum follow-up of ~4.5 years; median 5.3 years)
  - OS
  - DMFS analysis per IRC (DM event or death)
  - Updated safety

<table>
<thead>
<tr>
<th></th>
<th>Planned</th>
<th></th>
<th>Final</th>
<th></th>
<th>α level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Power</td>
<td>Events</td>
<td>Power</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>491</td>
<td>85%</td>
<td>376</td>
<td>76%</td>
<td>0.049</td>
</tr>
<tr>
<td>DMFS</td>
<td>523</td>
<td>90%</td>
<td>506</td>
<td>89%</td>
<td>0.042</td>
</tr>
</tbody>
</table>
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>0.76 (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>

CI = confidence interval.

Patients Alive and Without Recurrence (%)

- Ipilimumab: 41%
- Placebo: 30%

O N Number of patients at risk

<table>
<thead>
<tr>
<th>264475</th>
<th>283</th>
<th>217</th>
<th>184</th>
<th>161</th>
<th>77</th>
<th>13</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>323476</td>
<td>261</td>
<td>199</td>
<td>154</td>
<td>133</td>
<td>65</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

0 1 2 3 4 5 6 7 8 Year

PCPA 2017 Andrew Haydon
Patients Alive (%)

<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)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.72 (0.58, 0.88)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Stratified by stage provided at randomization.

OS

Survival curves for Ipilimumab (blue) and Placebo (red) showing OS (Overall Survival) rates of 65% and 54% respectively after 8 years.

- Patients at risk:
  - Ipilimumab: 162475
  - Placebo: 214476

*Graphical representation of patient survival data.*
## Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab (n = 471)</th>
<th>Placebo (n = 474)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<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><strong>45.4</strong></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><strong>90.4</strong></td>
<td>41.6</td>
</tr>
</tbody>
</table>

- No new deaths due to drug-related AEs compared with the primary analysis
  - 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 syndrome
  - No deaths related to study drug in the placebo group
Adjuvant Studies

- **COMBI-AD**
  - Dabraf + Tramet vs Placebo
- **BRIM8**
  - Vemurafenib vs Placebo
- **BMS**
  - Ipilimumab 10 vs Nivolumab
- **EORTC**
  - Pembrolizumab vs Placebo

All studies were double blinded and treatment was for 12 months.
New systemic treatments

Targeted therapies
Immunotherapies
Targeted Therapy in Melanoma
40%* of melanomas

RTK

RAS

BRAF\textsuperscript{V600mut}

MEK

ERK

ATP

Cellular Proliferation

Cellular Survival
Cellular Proliferation

RTK

RAF

Vemurafenib, Dabrafenib

Encorafenib

ATP

ERK

MEK

BRAF

V600mut

40%* of melanomas

RAS

40%* of melanomas

Cobimetinib, Trametinib, Binemtinib

Vemurafenib, Dabrafenib

Encorafenib

Cellular Survival

Cellular Proliferation
Single agent Braf inhibitors
Phase III BRIM-3 Study design

**Screening**
- BRAF<sup>V600E</sup> mutation

**Stratification**
- Stage
- ECOG PS (0 vs 1)
- LDH level (↑ vs nl)
- Geographic region

**Randomisation**
- N=675

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

**Dacarbazine**
- 1000 mg/m<sup>2</sup> iv q3w (N=338)

**Co-primary endpoints:**
- Overall Survival
- Progression Free Survival
BREAK-3: study design\(^1\)

**Eligibility criteria**
- Unresectable stage III/IV MM
- Treatment naive (except for IL-2)
- ECOG PS 0/1
- Stable CNS metastases
- BRAF V600E mutation

**Screened**
- n=733

**Enrolled**
- n=250

**3:1 randomisation**

- **TAFINLAR**
  - 150 mg b.d.
  - n=187

- **DTIC**
  - 1000 mg/m\(^2\)
  - IV q3w
  - n=63

**Crossover allowed at radiologic PD:**
- TAFINLAR 150 mg b.d.

**Primary endpoint:** Investigator-assessed PFS

**Secondary endpoints:** PFS assessed by IRC, OS, ORR in both groups and after crossover, PFS after crossover, DoR, QoL, safety/tolerability

TAFINLAR significantly extends PFS vs DTIC in patients with BRAF\textsuperscript{V600E} unresectable stage III or metastatic melanoma\textsuperscript{1-3}

Data cut-off June 2012

HR 0.37 (95% CI: 0.23, 0.57)
\(p<0.0001\)

TAFINLAR:
median PFS 6.9 months
median follow-up time 10.5 months

DTIC:
median PFS 2.7 months
median follow-up time 9.9 months

**Selected adverse events in BRIM 3 (% of patients)**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Vemurafenib, n=336</th>
<th>Dacarbazine, n=287</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>53</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>↑LFTs</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Cutaneous SCC</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Uveitis**</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Discontinuations due to AE: 7% vemurafenib; 4% dacarbazine
### Treatment-related AEs: ≥ 5% of patients

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib, n (%)</th>
<th>DTIC, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>95</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Palmar-plantar hyperkeratosis</td>
<td>39</td>
<td>4 (2)</td>
</tr>
<tr>
<td>SCC/KA</td>
<td>13</td>
<td>9 (5)</td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1</td>
<td>(&lt;1)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>30</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>32</td>
<td>–</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>26</td>
<td>–</td>
</tr>
</tbody>
</table>

Photosensitivity: dabrafenib (3%), DTIC (5%)
Well differentiated SCC
**METRIC: study design**

**Eligibility criteria**
- Unresectable stage III/IV MM
- Prior treatment allowed
- ECOG PS 0/1
- Stable CNS metastases
- BRAF V600E/K mutation

**Screened**
- \(n=1059\)

**Enrolled**
- \(n=322\)

**2:1 randomisation**
- **Trametinib 2mg O.D.**
  - \(n=214\)
- **Chemotherapy (DTIC or Paclitaxel)**
  - \(n=108\)

**Crossover allowed at radiologic PD:**
- Trametinib 2mg O.D.

**Primary endpoint:** PFS in Braf V600E mutated melanoma

**Secondary endpoints:** PFS in ITT, OS, ORR, safety/tolerability

A Progression-free Survival

Hazard ratio, 0.45 (95% CI, 0.33–0.63)  
P<0.001

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>108</th>
<th>87</th>
<th>43</th>
<th>24</th>
<th>21</th>
<th>10</th>
<th>6</th>
<th>1</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>108</td>
<td>87</td>
<td>43</td>
<td>24</td>
<td>21</td>
<td>10</td>
<td>6</td>
<td>1</td>
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</tr>
<tr>
<td>Trametinib</td>
<td>214</td>
<td>205</td>
<td>163</td>
<td>100</td>
<td>88</td>
<td>28</td>
<td>22</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Overall Survival

Hazard ratio for death, 0.54 (95% CI, 0.32–0.92)  
P=0.01

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Trametinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since Randomization</td>
<td>108</td>
<td>214</td>
</tr>
<tr>
<td>0</td>
<td>96</td>
<td>208</td>
</tr>
<tr>
<td>1</td>
<td>94</td>
<td>203</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>192</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>170</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>105</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>53</td>
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<td>6</td>
<td>15</td>
<td>24</td>
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<td>7</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Combination Braf + MEK inhibitors
Combination B-Raf + MEK inhibition

• **COMBI-v**
  – GSK/Novartis (Dabraf + Tramet vs Vem)
  – Primary end-point OS

• **COMBI-d**
  – GSK/Novartis (Dabraf + Tramet vs Dabraf)
  – Primary end-point PFS

• **CoBRIM**
  – Roche (Vem + Cobimet vs Vem)
  – Primary end-point PFS

• **COLUMBUS**
  – Novartis (Encorafenib + Bininetinib vs Vem)
COMBI-v

Study Design and Endpoints

N = 1,644 screened

- BRAF V600E/K mutation
- Stages IIIIC or IV cutaneous melanoma
- Treatment-naive in advanced or metastatic
- ECOG PS 0 or 1
- No brain metastases, unless
  - Treated
  - Stable > 12 weeks

Stratification
- BRAF V600E vs V600K mutation
- LDH (> ULN vs ≤ ULN)

Interim OS Analysis (n = 202)
Final OS Analysis (n = 288)

Dabrafenib (150 mg BID) + trametinib (2 mg daily)
(n = 352)

Vemurafenib (960 mg BID)
(n = 352)

Primary endpoint: OS
Secondary endpoints: progression-free survival (PFS), overall response rate (ORR), duration of response (DoR), safety
# Best Confirmed Response

<table>
<thead>
<tr>
<th>Best confirmed response</th>
<th>Dabrafenib + trametinib (n = 351)</th>
<th>Vemurafenib (n = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, n (%)</td>
<td>47 (13)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>179 (51)</td>
<td>153 (44)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>92 (26)</td>
<td>106 (30)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>22 (6)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Not evaluable, n (%)</td>
<td>11 (3)</td>
<td>26 (7)</td>
</tr>
<tr>
<td><strong>Response rate, n (%)</strong></td>
<td>226 (64)</td>
<td>180 (51)</td>
</tr>
<tr>
<td><strong>(95% CI)</strong></td>
<td>(59.1–69.4)</td>
<td>(46.1–56.2)</td>
</tr>
<tr>
<td><strong>Difference in ORR, % (95% CI)</strong></td>
<td>13 (5.7–20.2)</td>
<td></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>DoR, months (95% CI)</strong></td>
<td>13.8 (11.0–NR)</td>
<td>7.5 (7.3–9.3)</td>
</tr>
</tbody>
</table>

NR, not reached

26-30 September 2014, Madrid, Spain

esmo.org
Updated outcomes; COMBI-v: PFS and OS For Dabrafenib + Trametinib

**Progression-Free Survival**

- **Dabrafenib + trametinib (n = 352)**
  - Median PFS, 12.1 mo (95% CI, 9.7-14.7)

- **Vemurafenib (n = 352)**
  - Median PFS, 7.3 mo (95% CI, 5.7-7.8)
  - HR, 0.61 (95% CI, 0.51-0.73)

**Overall Survival**

- **Dabrafenib + trametinib (n = 352)**
  - Median OS, 26.1 mo (95% CI, 22.6-35.1)
  - 162 censored pts: 134 (83%) ongoing f/u, of which 66 (49%) are still on study tx

- **Vemurafenib (n = 352)**
  - Median OS, 17.8 mo (95% CI, 15.6-20.7)
  - 128 censored pts: 89 (70%) ongoing f/u, of which 10 (11%) are still on study tx
  - HR, 0.68 (95% CI, 0.56-0.83)

**Patients at risk, n**

- **D + T**
  - 352, 236, 162, 120, 93, 80, 63, 25

- **Vem**
  - 352, 162, 82, 55, 27, 16, 11, 2

---

**a** Intent-to-treat population; **b** Vemurafenib group includes 34 patients who crossed over to combination arm; +, censored.

3-year landmark analysis data cutoff: July 15, 2016. Median follow-up: D + T, 23.0 months; Vem, 15.0 months.

D, dabrafenib; Pbo, placebo; T, trametinib, Vem, vemurafenib.

Robert C, et al. ESMO 2016 [abstract LBA40].
COMBI-d

**Primary Endpoint:** investigator-assessed PFS

**Secondary Endpoints:** OS, overall response rate (ORR), duration of response, safety

**Presented by:** Keith T. Flaherty, MD

---

- **BRAF V600E/K**
- Unresectable stage IIIC/IV
- Treatment naive
- ECOG PS 0/1
- No brain metastases, unless:
  - Treated
  - Stable ≥ 12 weeks

**Stratification**
- **BRAF-mutant (V600E vs K)**
- LDH (> ULN vs ≤ ULN)

**Treatment Groups:**
- **Dabrafenib + trametinib**
  - 150 mg BID + 2 mg QD
  - n = 211
- **Dabrafenib + placebo**
  - 150 mg BID + placebo QD
  - n = 212

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

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

**Pre-planned interim OS**
- [95 events]

---

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; QD, once daily; ULN, upper limit of normal.
COMBI-d: PFS and OS

**Progression-Free Survival**
- **Dabrafenib + Trametinib (n = 211)**
  - HR, 0.67; \( P = 0.0004 \)
- **Dabrafenib + Placebo (n = 212)**
  - 2-\( y \) PFS, 30%
  - 2-\( y \) PFS, 16%
  - 3-\( y \) PFS, 22%
  - 3-\( y \) PFS, 12%

**Overall Survival**
- **Dabrafenib + Trametinib (n = 211)**
  - HR 0.71. \( p = 0.01 \)
  - 2-\( y \) OS, 52%
  - 3-\( y \) OS, 44%
- **Dabrafenib + Placebo (n = 212)**
  - 2-\( y \) OS, 43%
  - 3-\( y \) OS, 32%

---

\[ a \] Intent-to-treat population; \[ b \] Dabrafenib + placebo includes 26 patients who crossed over to combination arm; +, censored.

Presented by: Keith T. Flaherty, MD
coBRIM

Study Design

- Melanoma, unresectable locally advanced or metastatic (n = 495)
- BRAF<sup>V600</sup> mutation (cobas® 4800)
- No prior systemic therapy for advanced disease
- ECOG PS 0/1

1:1

Vemurafenib
960 mg BID × 28 days (days 1-28)
+ Cobimetinib
60 mg QD × 21 days (days 1-21)

Stratification
- Geographic region
- Extent of disease (M1c vs. other)

Vemurafenib
960 mg BID × 28 days (days 1-28)
+ Placebo

Disease progression, unacceptable toxicity, or withdrawal of consent

Primary end point
- PFS, investigator assessed

Secondary end points
- OS
- Objective response rate
- Duration of response
- PFS, IRC assessed
- Safety
- Pharmacokinetics
- Quality of life: QLQ-C30 and EQ-5D

Statistical assumptions
- 95% power to detect an improvement in median PFS from 6 to 11 months (HR = 0.55)
- 80% power to detect an improvement in median OS from 15 to 20 months (HR = 0.75)

BID, two times daily; ECOG, Eastern Cooperative Oncology Group; EQ, EuroQol; HR, hazard ratio; IRC, independent review committee; OS, overall survival; PS, performance status; QD, once daily; QLQ, quality of life questionnaire.
coBRIM Overall Survival

- **Cobimetinib and vemurafenib group**
  - Events, n (%): 141 (56.9%)
  - Median overall survival, months (95% CI): 17.4 (15.0–19.8)
  - Hazard ratio (95% CI): 0.70 (0.55–0.90); p=0.005

- **Placebo and vemurafenib group**
  - Events, n (%): 114 (46.2%)
  - Median overall survival, months (95% CI): 22.3 (20.3–NE)

- **Censored patients**

Number at risk:
- Cobimetinib and vemurafenib group: 247 → 232 → 210
- Placebo and vemurafenib group: 248 → 230 → 194

Larkin J et al. NEJM 2014
COLUMBUS

Study Design and Objectives

Part 1
Locally advanced unresectable or metastatic melanoma with BRAF V600 mutation

Randomized 1:1:1
N=577

ENCO 450 mg QD + BINI 45 mg BID (COMBO450)
n=192

ENCO 300 mg QD (ENCO300)
n=194

VEM 960 mg BID
n=191

Stratified by
- AJCC stage
- ECOG status
- BRAF mutation status/prior first-line immunotherapy

- Untreated or progressed on/after prior first-line immunotherapy
- BRAF V600E and/or V600K
- ECOG PS 0–1

Primary endpoint: PFS† for COMBO450 vs VEM
Key secondary endpoint (tested sequentially): PFS† for COMBO450 vs ENCO300
Patient-reported outcomes: FACT-M, EORTC QLQ-C30

- Key secondary endpoint of overall survival for COMBO450 vs VEM not yet mature
Progression-Free Survival: COMBO450 vs VEM

**Central Review**

![Graph showing progression-free survival (PFS) rates over time for COMBO450 and VEM.](image)

**Median PFS in months (95% CI)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS (95% CI)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMBO450</td>
<td>14.9 (11.0–18.5)</td>
<td>0.54 (0.41–0.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VEM</td>
<td>7.3 (5.6–8.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Local Review**

![Graph showing progression-free survival for COMBO450 and VEM.](image)

**Median PFS in months (95% CI)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS (95% CI)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMBO450</td>
<td>14.8 (10.4–18.4)</td>
<td>0.49 (0.37–0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VEM</td>
<td>7.3 (5.7–8.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Nominal P-value.

BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID
# BRAF Inhibitor-Related Adverse Events

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Dabrafenib + trametinib (n = 350)</th>
<th>Vemurafenib (n = 349)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF inhibitor-related AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>184 (53)</td>
<td>73 (21)</td>
</tr>
<tr>
<td>Cutaneous squamous-cell carcinoma and keratoacanthoma</td>
<td>5 (1)</td>
<td>63 (18)</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>15 (4)</td>
<td>86 (25)</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>6 (2)</td>
<td>80 (23)</td>
</tr>
<tr>
<td>Hand-Foot syndrome†</td>
<td>14 (4)</td>
<td>87 (25)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>20 (6)</td>
<td>137 (39)</td>
</tr>
<tr>
<td>Photosensitivity + sunburn</td>
<td>15 (4)</td>
<td>124 (36)</td>
</tr>
<tr>
<td>Non-cutaneous malignancy</td>
<td>3 (&lt; 1)</td>
<td>2 (&lt; 1)</td>
</tr>
<tr>
<td>New primary melanoma</td>
<td>2 (&lt; 1)</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>

*AEs indicated are those typically associated with BRAF inhibitors
†Hand–Foot syndrome = palmoplantar keratoderma and palmar plantar erythrodysaesthesia
If patient develops symptom(s) of possible treatment-related pyrexia syndrome

**DAY 1**
IMMEDIATELY STOP taking BOTH dabrafenib + trametinib

**DAY 2**
Has the patient’s symptoms improved?

Yes

No

**DAY 3**
Has the patient been symptom-free for ≥24 hours?

Yes

Has the patient’s symptoms continued to improve?

Yes

No

**DAY 5**
Has the patient been symptom-free for ≥24 hours?

Yes

No

**RESTARTING TREATMENT**
Always recommence treatment at the FULL dose – DO NOT reduce the dose of either drug.

REMEMBER:
Dose reduction appears to be an ineffective strategy for preventing pyrexia syndrome\(^1\) and also has the potential to compromise clinical outcome.\(^2\)

**PATIENT NEEDS A FULL AND IMMEDIATE MEDICAL ASSESSMENT**
Advertise the patient to make an urgent appointment to be properly assessed by a medical oncologist or to present immediately to a hospital Emergency Department if a medical oncologist not available (e.g., if it is after hours).

The assessment should include a work-up to exclude infection: full blood count (FBC), liver function tests (LFTs), electrolytes, urea, creatinine (EUC), clinical examination, chest x-ray, urine analysis and cultures.

Atkinson V et al. APJCO 2017
COMBI-d

Favorable Prognostic Factors: Dabrafenib + Trametinib

Baseline LDH ≤ ULN and < 3 Organ Sites With Metastasis

Progression-Free Survival

Overall Survival

From Flaherty K, et al. In: Proceedings from the American Society of Clinical Oncology; June 3-7, 2016; Chicago, IL [abstract 9502].

Any organ at baseline with ≥ 1 metastasis could be counted as a single disease site; +, censored. Flaherty KT, et al. ASCO 2016 [abstract 9502].
COMBI-v
Favorable Prognostic Factors: Dabrafenib + Trametinib

Baseline LDH ≤ ULN and < 3 met sites

Progression-Free Survival

Overall Survival

Robert C, et al. ESMO 2016 [abstract LBA40].
COMBI-v: OS and PFS for Patients With Baseline LDH > ULN

**OS, Baseline LDH > ULN**

- **Dabrafenib + Trametinib**
  - Median OS, 10.8 mo (95% CI, 8.9-14.4 mo)
- **Vemurafenib**
  - Median OS, 8.9 mo (95% CI, 7.3-10.7 mo)
  - HR, 0.81 (95% CI, 0.59-1.10)

**PFS, Baseline LDH > ULN**

- **Dabrafenib + Trametinib**
  - Median PFS, 5.5 mo (95% CI, 4.9-7.2 mo)
- **Vemurafenib**
  - Median PFS, 4.0 mo (95% CI, 3.7-5.4 mo)
  - HR, 0.70 (95% CI, 0.53-0.94)
Immunotherapy
MDX010-020: Phase 3, randomised, double-blind study in previously-treated advanced melanoma\(^1,2\)

### PRIMARY ENDPOINT
- Overall survival with ipilimumab plus gp100 vs. gp100 alone\(^3\)

### SECONDARY ENDPOINTS
- Overall survival with ipilimumab alone vs. gp100 alone\(^3\)
- Overall response rate\(^6\)
- Duration of response
- Progression-free survival

---

**Patients in whom new lesions developed or baseline lesions grew** were allowed to receive additional treatment to complete induction; patients with stable disease for 3 months’ duration after week 12 or a confirmed partial or complete response were offered additional courses of therapy if they had disease progression\(^1,2\).
MDX010-020: Overall survival in previously-treated, advanced melanoma (primary endpoint)\(^1,2\)

Overall survival in advanced melanoma: Kaplan-Meier estimate\(^1,2\)

- 34% reduction in the risk of death with ipilimumab monotherapy vs. gp100
  - HR=0.66; 95% CI 0.51–0.87; p=0.003\(^1,2\)
- 1-year overall survival rate was 44% for ipilimumab + gp100 and 46% for ipilimumab alone vs. 25% for gp100 alone\(^1,2\)
- No difference in overall survival was detected between both ipilimumab groups – secondary comparison, HR=1.04; p=0.76\(^1\)

Hodi S et al NEJM 2010
Pooled overall survival (OS) data from 12 studies using Ipilimumab in metastatic melanoma
Ipilimumab 10mg/Kg vs 3mg/Kg

Ascierto PA et al. Lancet Oncology 2017
Progression-Free Survival

**Total**
- Pts, N: 655
- Events, n: 482 (74%)
- Median (95% CI): 4.9 mo (3.1-5.5)

**Treatment Naive**
- Pts, N: 152
- Events, n: 100 (66%)
- Median (95% CI): 5.0 mo (3.7-14.0)
Keynote 001

Overall Survival

Total

<table>
<thead>
<tr>
<th>Pts, N</th>
<th>Events, n</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>655</td>
<td>358</td>
<td>24.4 mo (20.2-29.0)</td>
</tr>
</tbody>
</table>

Treatment Naive

<table>
<thead>
<tr>
<th>Pts, N</th>
<th>Events, n</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>152</td>
<td>72</td>
<td>32.2 mo (27.2-NR)</td>
</tr>
</tbody>
</table>

*Excludes patients with ocular melanoma. Analysis cutoff date: Sep 18, 2015.
Keynote 001 Pembrolizumab: Complete Responders Who Stopped Treatment for Observation (N = 61)

- 59 (97%) of responses were maintained

Unconfirmed progression; patient remains in follow-up
Confirmed progression; patient started second pembro course

Time (years)

Robert C et al ASCO 2016

Total bar length represents the time to the last scan.
Analysis cutoff date: Sep 18, 2015.
Nivolumab Monotherapy Phase I Trial
Overall Survival at 5 Years of Follow-up

All Patients (events: 69/107), median and 95% CI: 17.3 (12.5–37.8)

Probability of Survival

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>107</th>
<th>88</th>
<th>64</th>
<th>51</th>
<th>49</th>
<th>43</th>
<th>41</th>
<th>36</th>
<th>29</th>
<th>17</th>
<th>15</th>
<th>12</th>
<th>3</th>
<th>1</th>
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</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>107</td>
<td>88</td>
<td>64</td>
<td>51</td>
<td>49</td>
<td>43</td>
<td>41</td>
<td>36</td>
<td>29</td>
<td>17</td>
<td>15</td>
<td>12</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NIVO 3 mg/kg</td>
<td>17</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

AACR 2016 Annual Meeting Hodi et al. (Abstract CT001)
irAEs Are Associated With Immuno-oncology Therapies

The AEs described here represent some but not all irAEs that may occur with immune checkpoint inhibitor therapies.

Kinetics of Appearance of irAEs With Checkpoint Blockade

- Data from pts receiving anti–PD-1 antibodies q2w for ≥ 3 yrs show most irAEs occur by Wk 24 (6 mos)
- Toxicities with PD-1/PD-L1 agents may take longer to resolve than with ipilimumab, so long-term surveillance is recommended

PD-1 Ab superior to Chemotherapy

Keynote 002  
Checkmate 066
PD-1 is superior to Ipilimumab

Keynote 006
Checkmate 067: Progression-Free Survival
Ipilimumab vs Nivolumab OR Nivolumab + Ipilimumab N=945

- Nivolumab + Ipilimumab
  - 49% at 12 months
  - 46% at 18 months

- Nivolumab
  - 42% at 12 months
  - 39% at 18 months

- Ipilimumab
  - 18% at 12 months
  - 14% at 18 months

**Median PFS**
- 11.5 months for Nivolumab + Ipilimumab
- 6.9 months for Nivolumab
- 2.9 months for Ipilimumab

**HR vs Ipilimumab**
- Nivo: 0.55 (0.43-0.76)
- Nivo+Ipi: 0.42 (0.31-0.57)

Wolchok et al ASCO 2016
## 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
Is there a “plateau”? 

Keynote 006

Checkmate 066

Progression-Free Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab Q2W</td>
<td>181</td>
<td>0.61 (0.56-0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pembrolizumab Q3W</td>
<td>183</td>
<td>0.61 (0.56-0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>202</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Progression-free survival in BRAF WT advanced melanoma: Kaplan-Meier estimate. Median progression-free survival was 5.4 months (95% CI 3.7-12.2) with nivolumab, vs. 2.2 months (95% CI 1.8-2.5) with dacarbazine (HR=0.42; 95% CI 0.32-0.53; \( p=0.0001 \)).

\(^1\) p-value for 12-month and 24-month progression-free survival not reported.

References:
1. Atkins V et al: SWOG 1001. Phase III study of nivolumab monotherapy (3 mg/kg, Q2W) vs. dacarbazine (1000 mg/m², Q3W) in 413 treatment-naive BRAF wild-type advanced (unresectable stage III or metastatic stage IV) melanoma patients.
Checkmate 069 Phase 2 Ipi + Nivo vs Ipi

Progression Free Survival

Overall Survival
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

N=315

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

Treat until progression or unacceptable toxicity

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
### 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

Database lock: Sept 13, 2016, minimum f/u of 28 months
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, mo (95% CI)</td>
<td>NR</td>
<td>20.0 (17.1–24.6)</td>
<td></td>
</tr>
<tr>
<td>HR (98% CI) vs. IPI</td>
<td>0.55 (0.42–0.72)*</td>
<td>0.63 (0.48–0.81)*</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.88 (0.69–1.12)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*P<0.0001

Patients at risk:

- NIVO+IPI: 314, 292, 265, 247, 228, 221, 209, 200, 198, 192, 170, 49, 7, 0
- NIVO: 316, 292, 265, 244, 230, 213, 201, 191, 181, 175, 157, 55, 3, 0
- IPI: 315, 285, 254, 228, 205, 182, 164, 149, 136, 129, 104, 34, 4, 0

Database lock: Sept 13, 2016, minimum f/u of 28 months
OS by Tumor PD-L1 Expression, 5% Cutoff

**PD-L1 Expression Level <5%**

<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 (31.8–NR)</td>
<td>NR (23.1–NR)</td>
<td>18.5 (13.7–22.5)</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO</td>
<td>0.84 (0.63–1.12)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**PD-L1 Expression Level ≥5%**

<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>28.9 (18.1–NR)</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO</td>
<td>1.05 (0.61–1.83)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

- ORR of 56.2% for NIVO+IPI and 42.3% for NIVO
- ORR of 73.5% for NIVO+IPI and 58.8% for NIVO
Targeted therapy or Immunotherapy?

- **Efficacy**
  - Progression free Survival
  - Response Rates
  - Overall Survival

- **Toxicity**

- **Certain Subgroups**
  - High LDH
  - Tumour burden
# EFFICACY

<table>
<thead>
<tr>
<th>Targeted Therapy</th>
<th>ORR</th>
<th>CR</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMBI-v</td>
<td>66%</td>
<td>16%</td>
<td>12.1</td>
</tr>
<tr>
<td>COMBI-d</td>
<td>69%</td>
<td>17%</td>
<td>11.0</td>
</tr>
<tr>
<td>CoBRIM</td>
<td>68%</td>
<td>16%</td>
<td>12.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ipilimumab</th>
<th>ORR</th>
<th>CR</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keynote 006</td>
<td>13%</td>
<td>5%</td>
<td>2.8</td>
</tr>
<tr>
<td>Checkmate 067</td>
<td>19%</td>
<td>2.2%</td>
<td>2.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pembrolizumab</th>
<th>ORR</th>
<th>CR</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketnote 001</td>
<td>33%</td>
<td>10%</td>
<td>4.9</td>
</tr>
<tr>
<td>Keynote 001 Rx naïve</td>
<td>45%</td>
<td>14%</td>
<td>5.0</td>
</tr>
<tr>
<td>Keynote 006 q2/52</td>
<td>37%</td>
<td>12%</td>
<td>5.6</td>
</tr>
<tr>
<td>Keynote 006 q 3/52</td>
<td>36%</td>
<td>13%</td>
<td>4.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>ORR</th>
<th>CR</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>32%</td>
<td>N/R</td>
<td>5.0</td>
</tr>
<tr>
<td>Checkmate 067</td>
<td>44%</td>
<td>15%</td>
<td>6.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nivolumab + Ipilimumab</th>
<th>ORR</th>
<th>CR</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checkmate 067</td>
<td>59%</td>
<td>17%</td>
<td>11.5</td>
</tr>
<tr>
<td>Checkmate 069</td>
<td>59%</td>
<td>22%</td>
<td>N/R</td>
</tr>
</tbody>
</table>

Overall Survival in Melanoma

- 220: Dabrafenib + trametinib (n=54)
- COMBI-d: Dabrafenib + trametinib (n=211)
- COMBI-v: Dabrafenib + trametinib (n=352)
- CoBrim: Vemurafenib+Cobimetinib (n=247)
- CHECKMATE 069: Ipilimumab + Nivolumab (n=95)
- CHECKMATE 066: Nivolumab (n=210)
- KEYNOTE-006: Pembrolizumab (n=556)
- CA184-002: Ipilimumab (n=137)

©Georgina V Long

References:
2. Long GV, et al. JCO 2015;
8. Padovani AACR 2016
## TOXICITY

<table>
<thead>
<tr>
<th>Targeted Therapy</th>
<th>Grade 3/4</th>
<th>Leading to Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMBI-v</strong>¹</td>
<td>52%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>COMBI-d</strong>²</td>
<td>32%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>CoBRIM</strong>³</td>
<td>57%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Ipilimumab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keynote 006 <strong>⁴</strong></td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>Checkmate 067 <strong>⁵</strong></td>
<td>27%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketnote 001 <strong>⁶</strong></td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Keynote 006 q2/52 <strong>⁴</strong></td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td>Keynote 006 q3/52 <strong>⁴</strong></td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Nivolumab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checkmate 067 <strong>⁵</strong></td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Nivolumab + Ipilimumab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checkmate 067 <strong>⁵</strong></td>
<td>57%</td>
<td>39%</td>
</tr>
<tr>
<td>Checkmate 069 <strong>⁷</strong></td>
<td>51%</td>
<td>28%</td>
</tr>
</tbody>
</table>

---

ORR in Subgroups of Total Population

- Overall (581)
  - BRAFwt (442)
  - BRAFmut (133)
  - M1a (34)
  - M1b (77)
  - M1c (463)
- <2 lines prior therapy (318)
- ≥2 lines prior therapy (263)
- Prior chemotherapy (196)
- Prior Immunotherapy (159)
- Prior BRAF inhibitor (97)
- BTS <median (290)
- BTS ≥median (291)
- IPI-N (277)
- IPI-T (304)
- 2 mg/kg Q3W (143)
- 10 mg/kg Q3W (272)
- 10 mg/kg Q2W (166)
- Male (363)
- Female (218)
- Age <65 years (354)
- Age ≥65 years (227)
- ECOG PS 0 (385)
- ECOG PS 1 (195)
- Normal LDH (331)
- Elevated LDH (238)
- Brain metastases (49)
- No brain metastases (531)

Analysis cut-off date: October 18, 2014.
Factors affecting Overall Survival in Patients treated with Dabrafenib + Trametinib

- LDH Normal
  - N = 398
  - 1Y = 85%
  - 2Y = 67%
  - 3Y = 57%

- LDH ≥ ULN
  - N = 219
  - 1Y = 54%
  - 2Y = 25%
  - 3Y = 7%

- Disease Sites < 3
  - N = 237
  - 1Y = 90%
  - 2Y = 75%
  - 3Y = 70%

- Disease Sites ≥ 3
  - N = 161
  - 1Y = 76%
  - 2Y = 55%
  - 3Y = 38%

- LDH >1-2 × ULN
  - N = 149
  - 1Y = 60%
  - 2Y = 33%
  - 3Y = 9%

- LDH ≥ 2 × ULN
  - N = 70
  - 1Y = 40%
  - 2Y = 7%
  - 3Y = 7%

*a Regression tree analysis.

NE, not estimable.
Pembrolizumab: Best Response

438 individual metastases
N=27 pts, med f/u 68 wks

PR/SD/PD
median size 246 mm$^2$

CR
median size 80mm$^2$
SMALLER, $p<0.05$

CR Lesion $\rightarrow$ 1% subsequently progressed (2/230)
PD or new lesion at 1$^{st}$ scan $\rightarrow$ 5% had an objective response later (4/80)

Lyle M et al. ASCO 2014
BRAFi + MEKi: Best Response

135 individual metastases

- CR: 53%
- PR: 32%
- SD: 13%
- PD: 2%

CR lesions were smaller  p<0.001
Only 1 CR metastasis progressed

Primary Endpoint: Overall Survival

- BRAF V600E/K
- Unresectable stage IIIC/IV
- Treatment naive
- ECOG PS 0/1
- No brain metastases, unless:
  - Treated
  - Stable ≥ 12 weeks

At Progression

Final Analysis (OS)

Dabrafenib + trametinib
150 mg BID + 2 mg QD

Ipilimumab + Nivolumab x 4
Nivo

Dabrafenib + trametinib
150 mg BID + 2 mg QD

Ipilimumab + Nivolumab x 4
Nivo
SSequential COMBo Immuno and Target therapy (SECOMBIT) Study (NCT02631447)

- Prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) followed by combo target therapy (encorafenib/binimetinib) and vice-versa.

- Patients affected by metastatic melanoma BRAF V600 mutated.

- Sample size 230 pts.

**Endpoints:**

*Primary* – OS

*Secondary* – PFS, Total PFS (TPFS): the time to the second progression, % patients alive at 2-3 years, BORR; Duration of Response, Toxicity, Biomarkers study.

Steering Committee:

P.A. Ascierto (Chair)
R. Dummer
I. Melero
G. Palmieri

This study is designed as a phase II randomized trial with no formal comparative test.
Co-stimulatory receptors

Inhibitory molecules or CHECKPOINTS
T-Cell Response: Second Signal

Coactivation Signals
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Use agonistic mAbs to ↑ activation

TCR

Inhibitory Signals
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Use blocking mAbs to ↑ activation

T-Cell Stimulation

T-Cell Inhibition

New Treatments Have Vastly Improved Outcomes for Patients With Melanoma

First line, weighted averages.