Modern Management of Melanoma

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Laikou General Hospital
Limassol, 25JAN2020
The problem.....
Metastatic melanoma is a bad disease

“Melanoma is the tumor that gives cancer a bad name”

George Canellos, DFCI
Before the advent of targeted therapy and immune checkpoint inhibitors, survival outcomes in patients with advanced melanoma were poor, with 5-year overall survival (OS) rates <10%.

Approved agents for metastatic melanoma
- 1965 Hydroxyurea
- 1975 Dacarbazine
- 1998 High dose Interleukin
Where Have We Come From?

DTIC Chemotherapy

1-year OS = 30% - 35%

DTIC = dacarbazine; HDC = histamine dihydrochloride; IFN = interferon; IL-2 = interleukin 2; OS = overall survival.

Adapted from Middleton M, et al. Ann Oncol. 2007;18:1691-1697 (Figure 1) and Balch CM, et al. J Clin Oncol. 2001;19:3635-3648 (Figure 2).
High-Dose IL-2 Therapy

RR: 16% (43/270)

Durable responses
- Median: 8.9 mos
- CR: not reached

Melanoma Medical Oncologists – Super Models

We have this expression, christy and I. We don’t wake up for less than $10,000 a day.

Linda Evangelista
What have we learned?

• 5yr Survival
What have we learned?

Median PFS - Immunotherapy

- January ✔️
- February ✔️
- March ✔️
- April ✔️
- May ✔️
- June ✔️
- July
- August
- September ✗
- October ✗
- November ✗
- December ✗
What have we learned?
Median PFS - Targeted Therapy

- January
- February
- March
- April
- May
- June
- July
- August
- September
- October
- November
- December

?
Overall Survival at 5 Years of Follow-up
Nivolumumab

Database lock Oct 2015

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>NIVO 3 mg/kg</th>
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<tbody>
<tr>
<td>All Patients</td>
<td>107</td>
<td>17</td>
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<td>NIVO 3 mg/kg</td>
<td>86</td>
<td>15</td>
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<tr>
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<td>64</td>
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</table>

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)
5-year survival outcomes in patients (pts) with advanced melanoma treated with pembrolizumab (pembro) in KEYNOTE-001.

Figure 1. Kaplan-Meier Estimate of OS\textsuperscript{a} in the Total Population (A) and in Treatment-Naive Patients (B)
Kaplan-Meier Estimates of Overall Survival in the Total Study Population\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>HR\textsuperscript{c} (95% CI)\textsuperscript{c}</th>
<th>P Value\textsuperscript{d}</th>
<th>24-Month Rate\textsuperscript{b, %}</th>
<th>36-Month Rate\textsuperscript{b, %}</th>
<th>48-Month Rate\textsuperscript{b, %}</th>
<th>60-Month Rate\textsuperscript{b, %}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Median \textsuperscript{e} (95% CI), months</td>
<td>15.9 (13.3-22.0)</td>
<td>0.73 (0.61-0.88)</td>
<td>0.00049</td>
<td>42.1</td>
<td>37.8</td>
<td>33.6</td>
</tr>
<tr>
<td>Combined pembrolizumab</td>
<td>32.7 (24.5-41.6)</td>
<td></td>
<td></td>
<td></td>
<td>55.2</td>
<td>48.1</td>
<td>42.3</td>
</tr>
</tbody>
</table>

Median OS was 32.7 months (95% CI, 24.5-41.6) in the combined pembrolizumab arm (n = 556) and 15.9 months (95% CI, 13.3-22.0) in the ipilimumab arm (n = 278) (hazard ratio [HR], 0.73; P = 0.00049)

5-year OS rates were 38.7% in the combined pembrolizumab arm and 31.0% in the ipilimumab arm

ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1.

\textsuperscript{a}Patients excluded from the total population in the combined pembrolizumab and the ipilimumab arms had experienced progression with prior BRAF/MEK inhibitor (n = 95 [17.1%], n = 56 [20.1%]), prior chemotherapy (n = 77 [13.8%], n = 29 [10.4%]), or prior immunotherapy (n = 15 [2.7%], n = 12 [4.3%]).

\textsuperscript{b}From product-limit (Kaplan-Meier) method for censored data.

\textsuperscript{c}Based on Cox regression model with treatment as a covariate stratified by line of therapy (first vs second), PD-L1 status (positive vs negative), and ECOG PS (0 vs 1). If no patients are in 1 of the treatment groups involved in a comparison for a particular stratum, that stratum is excluded from the treatment comparison.

\textsuperscript{d}1-sided P value based on log-rank test.
For patients receiving first-line treatment, median OS was 38.7 months (95% CI, 27.3-50.7) in the combined pembrolizumab arm and 17.1 months (95% CI, 13.8-26.2) in the ipilimumab arm (HR, 0.73)
- 5-year OS rates were 43.2% in the combined pembrolizumab arm and 33.0% in the ipilimumab arm

ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1.

*Patients excluded from the total population in the combined pembrolizumab and the ipilimumab arms had experienced progression with prior BRAF/MEK inhibitor (n = 95 [17.1%], n = 56 [20.1%]), prior chemotherapy (n = 77 [13.8%], n = 29 [10.4%]), or prior immunotherapy (n = 15 [2.7%], n = 12 [4.3%]).

*From product-limit (Kaplan-Meier) method for censored data.

*Based on Cox regression model with treatment as a covariate stratified by line of therapy (first vs second), PD-L1 status (positive vs negative), and ECOG PS (0 vs 1). If no patients are in 1 of the treatment groups involved in a comparison for a particular stratum, that stratum is excluded from the treatment comparison.

*1-sided P value based on log-rank test.
Kaplan-Meier Estimates of PFS per irRC by Investigator Review in the Total Study Population

- Median PFS was 8.4 months (95% CI, 6.6-11.3) in the combined pembrolizumab arm and 3.4 months (95% CI, 2.9-4.2) in the ipilimumab arm (HR, 0.57; P = 0.00000)
  - 4-year PFS rates were 23.0% in the combined pembrolizumab arm and 7.3% in the ipilimumab arm

<table>
<thead>
<tr>
<th></th>
<th>PFS (95% CI, months)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>24-Month Ratio (%)</th>
<th>36-Month Ratio (%)</th>
<th>48-Month Ratio (%)</th>
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</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>3.4 (2.3-4.2)</td>
<td>0.57 (0.48-0.67)</td>
<td>0.00000</td>
<td>14.0</td>
<td>11.7</td>
<td>7.0</td>
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<tr>
<td>Combined</td>
<td>8.4 (6.6-11.3)</td>
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</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
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</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; irRC, immune-related response criteria; PD-L1, programmed death ligand 1; PFS, progression-free survival.

aFrom product-limit (Kaplan-Meier) method for censored data.

bBased on Cox regression model with treatment as a covariate stratified by line of therapy (first vs second), PD-L1 status (positive vs negative), and ECOG PS (0 vs 1). If no patients are in 1 of the treatment groups involved in a comparison for a particular stratum, that stratum is excluded from the treatment comparison.

c1-sided P value based on log-rank test.
Kaplan-Meier Estimates of PFS per irRC by Investigator Review in Patients Receiving First-Line Treatment

For patients receiving first-line treatment, median PFS was 11.6 months (95% CI, 8.2-16.4) in the combined pembrolizumab arm and 3.7 months (95% CI, 2.8-4.3; HR, 0.54) in the ipilimumab arm.

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>Median (95% CI, months)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>24-Month Rate, %</th>
<th>36-Month Rate, %</th>
<th>48-Month Rate, %</th>
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<tbody>
<tr>
<td>Ipiilimumab</td>
<td></td>
<td>3.7 (2.8-4.3)</td>
<td>0.64 (0.44-0.67)</td>
<td>0.00000</td>
<td>17.5</td>
<td>14.5</td>
<td>8.0</td>
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<tr>
<td>Combined</td>
<td></td>
<td>11.6 (8.2-16.4)</td>
<td></td>
<td></td>
<td>57.3</td>
<td>33.1</td>
<td>20.9</td>
</tr>
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ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; irRC, immune-related response criteria; PD-L1, programmed death ligand 1; PFS, progression-free survival.

*a* From product-limit (Kaplan-Meier) method for censored data.

*b* Based on Cox regression model with treatment as a covariate stratified by line of therapy (first vs second), PD-L1 status (positive vs negative), and ECOG PS (0 vs 1). If no patients are in 1 of the treatment groups involved in a comparison for a particular stratum, that stratum is excluded from the treatment comparison.

*c* 1-sided *P* value based on log-rank test.
Disposition of Patients Who Completed 2 Years of Pembrolizumab Therapy

- Of the 556 patients who received pembrolizumab, 103 (18.5%) completed 2 years of treatment; 76 (73.8%) were progression free and 27 (26.2%) had progressive disease.
- Responses were ongoing in most of the patients who experienced CR (76.2%) or PR (76.8%) and in 53.8% of patients with SD.

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CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

*a*Includes one patient who discontinued early with complete response and then progressed.
Interpretation of Keynote-006 and Keynote-002 results

• Treatment with anti-PD1 in first line
• Treatment may stop at 2 years (no data available for continuation)
• Nature of response is related with PFS and survival
• Rechallenge is feasible and may be used in every day practice
Overall Survival Checkmate 067

- Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

<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 (38.2–NR)</td>
<td>36.9 (28.2–58.7)</td>
<td>19.9 (16.8–24.6)</td>
</tr>
<tr>
<td>HR (95% CI) vs IPI</td>
<td>0.52 (0.42–0.64)</td>
<td>0.63 (0.52–0.76)</td>
<td>–</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO</td>
<td>0.83 (0.67–1.03)</td>
<td>–</td>
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</table>

HR = 0.83 (95% CI, 0.67–1.03)


ESMO 2019
Progression-Free Survival Checkmate 067

- Improved PFS with NIVO+IPI and NIVO vs IPI over 5 years

<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 (5.1–10.2)</td>
<td>2.9 (2.8–3.2)</td>
</tr>
<tr>
<td>HR (95% CI) vs IPI</td>
<td>0.42 (0.35–0.51)</td>
<td>0.53 (0.44–0.64)</td>
<td>–</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO*</td>
<td>0.79 (0.64–0.96)</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

*Descriptive analysis.

ESMO 2019
OS in Patients With *BRAF*-Mutant and Wild-Type Tumors Checkmate 067

- Improved OS and PFS with NIVO+IPI and NIVO vs IPI regardless of *BRAF* mutation status

### NIVO+IPI (n = 103)  NIVO (n = 98)  IPI (n = 100)

<table>
<thead>
<tr>
<th></th>
<th>Median, mo (95% CI)</th>
<th>HR (95% CI) vs IPI</th>
<th>HR (95% CI) vs NIVO*</th>
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<tbody>
<tr>
<td><strong>BRAF Mutant</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>NR (50.7–NR)</td>
<td>0.44 (0.30–0.64)</td>
<td>0.70 (0.46–1.05)</td>
</tr>
<tr>
<td><strong>BRAF Wild-Type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39.1 (27.5–NR)</td>
<td>0.57 (0.45–0.73)</td>
<td>0.89 (0.69–1.15)</td>
</tr>
</tbody>
</table>

- 5-year PFS rates of 38% (NIVO+IPI), 22% (NIVO), and 11% (IPI)

*Descriptive analysis.*

- 5-year PFS rates of 35% (NIVO+IPI), 32% (NIVO), and 7% (IPI)

ESMO 2019
OS by LDH Level

- Improved OS with NIVO+IPI and NIVO vs IPI regardless of baseline LDH levels

### LDH ≤ ULN

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (n = 199)</th>
<th>NIVO (n = 197)</th>
<th>IPI (n = 194)</th>
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<tbody>
<tr>
<td>Median, mo (95% CI)</td>
<td>NR</td>
<td>NR (40.2–NR)</td>
<td>28.8 (22.7–34.0)</td>
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<tr>
<td>HR (95% CI) vs IPI</td>
<td>0.48 (0.37–0.64)</td>
<td>0.58 (0.44–0.76)</td>
<td>–</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO*</td>
<td>0.83 (0.62–1.12)</td>
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### LDH > ULN

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<tr>
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<th>NIVO+IPI (n = 114)</th>
<th>NIVO (n = 112)</th>
<th>IPI (n = 115)</th>
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<tbody>
<tr>
<td>Median, mo (95% CI)</td>
<td>17.4 (10.7–42.6)</td>
<td>16.0 (11.7–21.7)</td>
<td>10.9 (8.4–13.1)</td>
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<tr>
<td>HR (95% CI) vs IPI</td>
<td>0.58 (0.43–0.79)</td>
<td>0.71 (0.53–0.96)</td>
<td>–</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO*</td>
<td>0.82 (0.59–1.13)</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

*Descriptive analysis. LDH, lactate dehydrogenase; ULN, upper limit of normal.
Dabrafenib Plus Trametinib: 5-Year OS

- **2-year, 52%** (95% CI, 48%-57%)
- **3-year, 44%** (95% CI, 40%-48%)
- **4-year, 37%** (95% CI, 33%-42%)
- **5-year, 34%** (95% CI, 30%-38%)

**Events, n (%)**
- Dabrafenib plus trametinib (n = 563)
  - 351 (62)

**Median OS (95% CI), mo**
- 25.9 (22.6-31.5)
Dabrafenib Plus Trametinib: OS by Baseline LDH Level

No. at risk
LDH ≤ ULN 366 348 299 252 226 201 185 171 154 145 138 91 14 0
LDH > ULN 196 151 92 62 43 36 34 30 27 24 23 12 2 0

Months Since Randomization

LDH Level ≤ ULN > ULN
2-year, 65% 2-year, 27%
3-year, 55% 3-year, 22%
4-year, 48% 4-year, 17%
5-year, 43% 5-year, 16%
Dabrafenib Plus Trametinib: OS in Patients With Normal LDH and < 3 Organ Sites

OS Probability

Months Since Randomization

No. at risk

2-year, 75%
3-year, 67%
4-year, 58%
5-year, 55%

LDH ≤ ULN and < 3 organ sites

Paul Nathan
Dabrafenib Plus Trametinib: 5-Year PFS

No. at risk

<table>
<thead>
<tr>
<th>Months Since Randomization</th>
<th>Dabrafenib plus trametinib (n = 563)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>Median PFS (95% CI), mo</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>2-year, 31% (95% CI, 27%-35%)</td>
<td>417 (74)</td>
</tr>
<tr>
<td>3-year, 24% (95% CI, 20%-28%)</td>
<td>363 (65)</td>
</tr>
<tr>
<td>4-year, 21% (95% CI, 17%-24%)</td>
<td>317 (56)</td>
</tr>
<tr>
<td>5-year, 19% (95% CI, 15%-22%)</td>
<td>235 (46)</td>
</tr>
</tbody>
</table>
Dabrafenib Plus Trametinib: PFS by Baseline LDH Level

LDH Level
≤ ULN
> ULN

PFS Probability

No. at risk
LDH ≤ ULN 366
LDH > ULN 196

Months Since Randomization
24
36
48
60
72
84
96
108
120
132
144
156
168
2
0

2-year, 39%
3-year, 31%
4-year, 27%
5-year, 25%
2-year, 14%
3-year, 9%
4-year, 8%
5-year, 8%

Paul Nathan

LDH Level
≤ ULN
> ULN

PFS Probability
Dabrafenib Plus Trametinib: PFS in Patients With Normal LDH and < 3 Organ Sites

PFS Probability

Months Since Randomization

No. at risk

2-year, 46%

3-year, 39%

4-year, 33%

5-year, 31%

LDH ≤ ULN and < 3 organ sites
Evaluation of Combination Treatment With Cobimetinib Plus Atezolizumab Versus Pembrolizumab in Previously Untreated Patients With Wild Type $BRAF^{V600}$ Advanced Melanoma: Primary Analysis From the Phase 3 IMspire170 Trial

Ana Arance\(^1\); Helen Gogas\(^2\); Brigitte Dréno\(^3\); Keith Flaherty\(^4\); Lev Demidov\(^5\); Daniil Stroyakovskiy\(^6\); Zeynep Eroglu\(^7\); Pier Francesco Ferrucci\(^8\); Jacopo Pigozzo\(^9\); Piotr Rutkowski\(^10\); Jacek Mackiewicz\(^11\); Isabelle Rooney\(^12\); Athina Voulgari\(^13\); Sarah Troutman\(^12\); Bethany Pitcher\(^14\); Yibing Yan\(^12\); James Larkin\(^15\)

\(^1\)Department of Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; \(^2\)First Department of Medicine, National and Kapodistrian University of Athens, Athens, Greece; \(^3\)C.H.R.U Hotel Dieu, Nantes, France; \(^4\)Massachusetts General Hospital, Boston, Massachusetts, USA; \(^5\)Russian Oncological Research Centers, Moscow, Russia; \(^6\)Moscow City Oncology Hospital, Moscow, Russia; \(^7\)Moffitt Cancer Center, Tampa, Florida, USA; \(^8\)European Institute of Oncology – IRCCS, Milan, Italy; \(^9\)Melanoma Oncology Unit, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy; \(^10\)Maria Sklodowska-Curie Institute – Oncology Center, Warsaw, Poland; \(^11\)University of Medical Sciences in Poznań, Poznań, Poland; \(^12\)Genentech, Inc., South San Francisco, California, USA; \(^13\)Roche Products Ltd., Welwyn Garden City, United Kingdom; \(^14\)Hoffmann-La Roche Ltd., Mississauga, Ontario, Canada; \(^15\)Royal Marsden NHS Foundation Trust, London, United Kingdom
**IMspire170: A Phase 3, Open-label, Multicenter, Randomised Study**

**Advanced melanoma**
N = 446

**Key eligibility criteria**
- Unresectable locally advanced or metastatic
- BRAF^{V600} WT
- Previously untreated
  - Adjuvant IFNα, IL-2, vaccine or ipilimumab allowed
- Measurable disease per RECIST v1.1
- Archival tissue or fresh biopsy

**Stratification factors**
- PD-L1 status (IC0 vs IC1/2/3)^a
- LDH (≤ULN vs >ULN)
- Geographic location (North America vs Europe vs Australia/New Zealand/others)

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^aAssessed using an anti–human PD-L1 rabbit monoclonal antibody (SP142; Ventana Medical Systems).
IC, immune cell; IFNα, interferon alpha; IL-2, interleukin-2; INV, investigator; IRC, independent review committee; IV, intravenous; LDH, lactate dehydrogenase; PO, per oral; q2w, every 2 weeks; q3w, every 3 weeks; ULN, upper limit of normal.
 IRC-Assessed PFS (Primary Endpoint) Impire 170

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Cobi + Atezo</th>
<th>Pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months (95% CI)</td>
<td>5.5 (3.8–7.2)</td>
<td>5.7 (3.7–9.6)</td>
</tr>
<tr>
<td>Hazard ratioa (95% CI)</td>
<td>1.15 (0.88–1.50); P=0.295</td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff: April 15, 2019; median follow-up duration: 7.0 months (range, 0–15).

aStratified by PD-L1 status and baseline LDH level. CI, confidence interval; IRC, independent review committee; NE, not estimable.
First Interim Overall Survival ImSpire 170

Data cutoff: April 15, 2019; median follow-up duration: 7.0 months (range, 0–15). *Stratified by PD-L1 status and baseline LDH level.
Updated Survival In Patients With BRAF-mutant Melanoma Administered Pembrolizumab, Dabrafenib, And Trametinib

Pier F. Ferrucci1a, Paolo A. Ascierto2a, Michele Maio3, Michele Del Vecchio4, Victoria Atkinson5, Inge Marie Svane1, Michael Lotem12, Mahmoud Abu-Anna13, Eduard Gasal14, Scott J. Diede15, Elizabeth Cloyd16, Henrik Schmiid6, Jacob E. Schachter7, Paola Queirolo8, Georgina V. Long9, Rosalie Stephens10, Michal Lotem12, Razi Ghori15, Scott J. Diede15, Elizabeth Cloyd16

Both authors contributed equally
KEYNOTE-022 Part 3 Study Design (NCT02130466)

**Patients**
- Histologically confirmed unresectable or metastatic stage IV $\textit{BRAF}^{V600E/K}$-mutant melanoma
- No prior therapy
- Measurable disease
- ECOG PS 0/1

**Stratification factors**
- ECOG PS (0 vs 1)
- LDH level ($>1.1 \times \text{ULN}$ vs $\leq 1.1 \times \text{ULN}$)

**Treatment arms**
- Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD for up to 2 y$^b$
- Placebo Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD for up to 2 y$^b$

**Study design**
- R (1:1)
- N = 120
- N = 60
- N = 60

**Primary end point:** PFS
**Secondary end points:** ORR, DOR, and OS
**Data cutoff:** Jun 26, 2019

---

*a Owing to the small number of patients enrolled in the ECOG PS 1 and LDH $\leq 1.1 \times \text{ULN}$ strata, these strata were combined.

*b Trametinib and/or dabrafenib could be continued beyond 2 y per standard of care.
Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + D + T</td>
<td>16.9 (11.3-27.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Placebo + D + T</td>
<td>10.7 (7.2-16.8)</td>
<td>0.34-0.83</td>
</tr>
</tbody>
</table>

*Based on Kaplan-Meier estimate of PFS, per investigator assessment.

*Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs ≤1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Data cutoff: Jun 26, 2019.
Kaplan-Meier Analysis of Duration of Response

Confirmed response based on investigator assessment per RECIST v1.1.

From Kaplan-Meier method for censored data.

Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Data cutoff: Jun 26, 2019.

<table>
<thead>
<tr>
<th>DOR (95% CI)b, mo</th>
<th>HR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + D + T</td>
<td>25.1 (14.1-NR)</td>
</tr>
<tr>
<td>Placebo + D + T</td>
<td>12.1 (6.0-15.7)</td>
</tr>
</tbody>
</table>

No. at risk:

- Pembro + D + T: 38 37 34 30 29 24 20 19 17 17 15 14 11 9 8 8 6 2 1 0
- Placebo + D + T: 43 42 33 27 23 22 21 16 13 9 7 7 6 4 3 3 2 2 1 0

24-mo rate:

- Pembro + D + T: 55%
- Placebo + D + T: 16%
Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>Median\textsuperscript{a} (95% CI), mo</th>
<th>HR\textsuperscript{b} (95% CI)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab + Durvalumab + Tremelimumab</td>
<td>26 (43.3)</td>
<td>NR (23.9-NR)</td>
<td>0.64 (0.38-1.06)</td>
</tr>
<tr>
<td>Placebo + Durvalumab + Tremelimumab</td>
<td>36 (60.0)</td>
<td>26.3 (18.2-NR)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Based on Kaplan-Meier estimate of overall survival.

\textsuperscript{b}Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN; owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Data cutoff: Jun 26, 2019.
NCCN Guidelines Version 1.2020
Cutaneous Melanoma

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

FIRST-LINE THERAPY

- Preferred regimens
  - Anti PD-1 monotherapy
    - Pembrolizumab (category 1)
    - Nivolumab (category 1)
    - Nivolumab/ipilimumab (category 1)
  - Combination targeted therapy if BRAF V600-activating mutation; preferred if clinically needed for early response
    - Dabrafenib/trametinib (category 1)
    - Vemurafenib/cobimetinib (category 1)
    - Encorafenib/binimetinib (category 1)

SECOND-LINE OR SUBSEQUENT THERAPY

- Systemic therapy
  - Preferred regimens
    - Anti PD-1 monotherapy
      - Pembrolizumab
      - Nivolumab
    - Nivolumab/ipilimumab
  - Combination targeted therapy if BRAF V600-activating mutation
    - Dabrafenib/trametinib
    - Vemurafenib/cobimetinib
    - Encorafenib/binimetinib
  - Other regimens
    - Ipilimumab
    - High-dose IL-2
  - Useful in certain circumstances
    - Ipilimumab/Intralesional T-VEC (category 2B)
    - Cytotoxic agents
    - Imatinib for tumors with activating mutations of KIT
    - Larotrectinib or entrectinib for NTRK gene fusion positive tumors
    - Binimetinib for NRAS mutated tumors that have progressed after prior immune checkpoint inhibitor therapy (category 2B)

- Consider best supportive care for poor performance status (See NCCN Guidelines for Palliative Care)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Lessons we need to learn

• Immunotherapy vs targeted therapy in BRAF(+) patients
• Combination of immunotherapy and targeted therapy vs targeted therapy
• Biomarkers
First line immunotherapy in BRAF positive patients

Results from randomized trials will answer the question
What's next?

• Changes in standard of care expected
  - Nivolumab + ipilimumab combination regimen

1st line role in patients with BRAF mutations
  - Anti-PD + MEK + BRAF inhibition
  - BRAF + MEK inhibition vs Anti-CTLA4 Anti-PD1
  - Anti-PD1 + T-VEC
  - Anti-PD1 + IDO1 inhibitor

Perspectives on Advanced Melanoma Treatment

Presented at ECC 2015

**SEquential COMBo Immuno and Target therapy (SECOMBIT) Study (NCT02631447)**

- Prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (pembrolizumab/nivolumab) followed by combo target therapy (encorafenib/binimetinib) and vice-versa
- Patients affected by metastatic melanoma BRAF V600 mutated
- Sample size 230 pts

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.

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

www.clinicaltrial.gov
Ipilimumab + nivolumab before/after dabrafenib + trametinib (NCT02224781)

- Randomised phase III study to evaluate the efficacy of treatment with ipilimumab and nivolumab followed by dabrafenib and trametinib and vice versa to determine the best sequential approach
- Patients with confirmed BRAF V600-mutated metastatic melanoma
- Sample size: 300 pts
- Final analysis: July 2019

Endpoints:
Primary – OS
Secondary – PFS, response rate, toxicity

ARM A
Nivolumab + ipilimumab

ARM B
Dabrafenib and trametinib

ARM C
Dabrafenib and trametinib

ARM D
Nivolumab and ipilimumab

Cross over to Arm C
Cross over to Arm D

Principal investigator: Dr. Michael Atkins
Cobimetinib plus vemurafenib followed by atezolizumab (EUDRACT 2015-005097-37)

- A phase II trial evaluating the efficacy and safety of a sequencing schedule of cobimetinib plus vemurafenib followed by atezolizumab and vice versa for treatment in patients with unresectable or metastatic melanoma
- Patients with confirmed \(\text{BRAF}^{V600}\)-mutated metastatic melanoma
- Sample size: 172 pts
- First patient enrolled: QIII 2016
- Final analysis: QI 2020

Endpoints:
- **Primary** – Time to Second Objective Disease Progression (PFS2) defined as time from start of run-in phase (date of first intake of study drug) to second objective disease progression according to RECIST v. 1.1. (PD2) following randomization or death from any cause
- **Secondary** – Safety, OS, OS rate at 12 and 24 months, 12-months and 24-months DCR, rate of patients with progressive disease who could not cross-over to subsequent line of therapy due to deterioration of ECOG status and/or brain metastases, PFS1 and PFS3

Principal investigator: Prof Dr. Dirk Schadendorf
Combination of immunotherapy and BRAF + MEK inhibition as first line in BRAF mutated

Results from randomized trials will answer the question
TRILOGY: Phase III Study Design

Stratification: Disease Stage & Geographic Location

Primary Endpoint
- Investigator Assessed PFS

Secondary Endpoints
- OS, ORR, DOR, Safety, PK

Exploratory Endpoints
- QoL, Biomarkers (PDL1, CD8+)

28-day run-in

Tx until PD or toxicity

Tumour assessment 8 weeks post - baseline and 8 weekly until PD

FPI Q1 2017
Basel, 13 December 2019

Roche announces positive Phase III study results for Tecentriq plus Cotellieic and Zelboraf in people with previously untreated BRAF V600 mutation-positive advanced melanoma

Late breaking abstract AACR
COMBI-i: Study Design for the part 3 Randomized Portion

**N = 500**

Unresectable or metastatic BRAF V600–mutant melanoma (stage III/IV)
- Previously untreated
- No active brain metastasis
- ECOG PS ≤ 2

Randomization stratification
- ECOG PS (0 vs 1 vs 2)
- LDH (< 1 × ULN vs ≥ 1 to < 2 × ULN vs ≥ 2 × ULN)

- Placebo IV
- Dabrafenib 150 mg BID + trametinib 2 mg QD
- PDR001 (RP3R identified in Part 1)
- Dabrafenib 150 mg BID + trametinib 2 mg QD

Primary: PFS (per RECIST v1.1)

Secondary: OS, ORR, DOR, DCR, safety, PRO, PK, PFS (per RECIST v1.1) and OS by PD-L1 status

*Treatment beyond PDRECIST is permitted if all of following criteria are met: (1) patient provides informed consent for treatment beyond progression, (2) the treatment will not delay an imminent intervention to prevent serious complications, (3) tolerance of study treatment, and (4) stable performance status.

The beginning of a new era in adjuvant treatment
The day that changed how we treat melanoma!

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma


Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma


09/11/2017
6 months later

Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

Alexander M.M. Eggermont, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Mario Mandala, M.D., Georgina V. Long, M.D., Ph.D., Victoria Atkinson, M.D., Stéphane Dalle, M.D., Andrew Haydon, M.D., Mikhail Lichinitser, M.D., Adnan Khattak, M.D., Matteo S. Carlino, M.D., Ph.D., Shahneen Sandhu, M.D., James Larkin, M.D., Susana Puig, M.D., Ph.D., Paolo A. Ascierto, M.D., Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D., Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D., Alfonso J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D., Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D., Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suciu, Ph.D., and Caroline Robert, M.D., Ph.D.
Primary Endpoint: RFS

% Recurrence-free Survival

Months

Number of patients at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>453</td>
<td>453</td>
</tr>
<tr>
<td>3</td>
<td>399</td>
<td>364</td>
</tr>
<tr>
<td>6</td>
<td>353</td>
<td>314</td>
</tr>
<tr>
<td>9</td>
<td>332</td>
<td>269</td>
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<td>12</td>
<td>311</td>
<td>252</td>
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<td>15</td>
<td>291</td>
<td>225</td>
</tr>
<tr>
<td>18</td>
<td>249</td>
<td>184</td>
</tr>
<tr>
<td>21</td>
<td>71</td>
<td>56</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NIVO Events/patients: 154/453

IPI Events/patients: 206/453

Median (95% CI): NIVO NR, IPI NR (16.6, NR)

HR (97.5% CI): NIVO 0.65 (0.51, 0.83), IPI NR

Log-rank P value: NIVO <0.0001
RELAPSE-FREE SURVIVAL (PRIMARY ENDPOINT)

No. at Risk
Dabrafenib plus trametinib
Placebo
NR, not reached.

Group | Events, n (%) | Median (95% CI), mo | HR (95% CI)
---|---|---|---
Dabrafenib plus trametinib | 166 (38) | NR (44.5-NR) | 0.47 (0.39-0.58); P < .001
Placebo | 248 (57) | 16.6 (12.7-22.1) | P = .0000000000000153

Dabrafenib plus trametinib
Placebo

P = .0000000000000153

Dabrafenib plus trametinib
Placebo

NR, not reached.
OVERALL SURVIVAL (FIRST INTERIM ANALYSIS)

No. at Risk

Dabrafenib plus trametinib
438 426 416 414 408 401 395 387 381 376 370 366 362 352 328 301 291 233 180 164 105 82 67 28 12 5 0 0

Placebo
432 425 415 410 401 386 378 362 346 337 328 323 303 284 269 252 202 164 152 94 64 51 17 7 1 0 0

a Prespecified significance boundary ($P = .000019$).
Recurrence-Free Survival in the ITT Population

Primary endpoint

% alive and recurrence-free

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Total Event</th>
<th>HR (98.4% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>135</td>
<td>0.57 (0.43-0.74)</td>
</tr>
<tr>
<td>Placebo</td>
<td>216</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Stratified Logrank P-value: <.0001

Patients at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Pembrolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>514</td>
<td>505</td>
</tr>
<tr>
<td>3</td>
<td>438</td>
<td>415</td>
</tr>
<tr>
<td>6</td>
<td>413</td>
<td>363</td>
</tr>
<tr>
<td>9</td>
<td>392</td>
<td>323</td>
</tr>
<tr>
<td>12</td>
<td>313</td>
<td>264</td>
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<td>15</td>
<td>182</td>
<td>157</td>
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<td>18</td>
<td>73</td>
<td>60</td>
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<td>21</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Stratified by stage given at randomization

HR 0.57

L. Eggermont AACR 2018

EORTC

The future of cancer therapy

Do not duplicate or distribute without permission from the author and ESO
Why did we succeed?

- Survival benefit of anti-PD1 agents had been proven
- Activity of anti-PD1 agents in metastatic melanoma is high
- Patients were stratified and staged homogenously
- Mode of action is clear
- Endpoints of trials were universal
Approvals

FDA

• **Nivolumab** was approved by the US Food and Drug administration (FDA) in **December 2017** for adjuvant treatment of patients who had undergone definitive resection of a cutaneous melanoma and had metastatic lymph node involvement, and for patients with stage IV disease who had undergone definitive resection of all sites of disease.

• On **February 15, 2019**, the Food and Drug Administration (FDA) approved **pembrolizumab** for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

EMA

• **Nivolumab** - 28 June 2018
• **Pembrolizumab** – 22 October 2018
What is the 5yr risk of recurrence and death for stage III

Data from **EORTC 18071** (Enrollment Period: June 2008 to July 2011)

Data from **AJCC 8th** (Enrollment Period:1998 to 2014)
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>

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

Patients Alive and Without Recurrence (%)

<table>
<thead>
<tr>
<th>Years</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>ON</td>
<td>O</td>
<td>N</td>
<td>Number of patients at risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
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<td>-----------------------------</td>
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<td>264475</td>
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<td>77</td>
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</tr>
<tr>
<td>323476</td>
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<td>476</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>
Patients Alive (%)

<table>
<thead>
<tr>
<th>Stratifed by stage provided at randomization.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iplilimumab</td>
</tr>
<tr>
<td>Deaths/patients</td>
</tr>
<tr>
<td>HR (95.1% CI)^a</td>
</tr>
<tr>
<td>Log-rank P value^a</td>
</tr>
</tbody>
</table>

OS

Number of patients at risk

<table>
<thead>
<tr>
<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 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>162475</td>
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<tr>
<td>214476</td>
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<td>348</td>
<td>297</td>
<td>273</td>
<td>178</td>
<td>58</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

*Stratified by stage provided at randomization.
Why do we need Adjuvant Treatment?

• The majority of patients with metastatic disease succumb to their disease
• 65-80% of patients have progressed at 5 years
Adjuvant Nivolumab Versus Ipilimumab in Resected Stage III/IV Melanoma: 3-Year Efficacy and Biomarker Results From the Phase 3 CheckMate 238 Trial

Jeffrey Weber,1 Michele Del Vecchio,2 Mario Mandala,3 Helen Gogas,4 Ana M. Arance,5 Stéphane Dalle,6 C. Lance Cowey,7 Michael Schenker,8 Jean-Jacques Grob,9 Vanna Chiarion-Sileni,10 Iván Márquez-Rodas,11 Marcus Butler,12 Michele Maio,13 Hao Tang,14 Abdel Saci,14 Veerle de Pril,14 Maurice Lobo,14 James Larkin,15* Paolo A. Ascierto16*

1NYU Perlmutter Cancer Center, New York, NY, USA; 2Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 3Papa Giovanni XIII Hospital, Bergamo, Italy; 4National and Kapodistrian University of Athens, Athens, Greece; 5Hospital Clínico de Barcelona, Barcelona, Spain; 6Hospices Civils de Lyon, Pierre Bénite, France; 7Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; 8Oncology Center Sf Nectarie Ltd., Craiova, Romania; 9Hôpital de la Timone, Marseille, France; 10Veneto Institute of Oncology IOV – IRCCS, Padua, Italy; 11General University Hospital Gregorio Marañón & CIBERONC, Madrid, Spain; 12Princess Margaret Cancer Centre, Toronto, ON, Canada; 13Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; 14Bristol-Myers Squibb, Princeton, NJ, USA; 15The Royal Marsden NHS Foundation Trust, London, UK; 16Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy

*Contributed equally.
CheckMate 238: Study Design

Patients with:
- High-risk, completely resected stage IIIB/IIIC or stage IVa melanoma
- No prior systemic therapy
- ECOG PS 0/1

Primary endpoint: RFS

Stratified by:
1) Disease stage: IIIB/IIIC vs IV M1a or M1b vs IV M1c
2) Tumor PD-L1 status at a 5% cutoff

NCT02388906.


Follow-up
Maximum treatment duration of 1 year

Database lock: January 31, 2019; minimum follow-up of 36 months for all patients

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

n = 453
n = 453
Primary Endpoint: RFS in All Patients

<table>
<thead>
<tr>
<th>Events, n</th>
<th>NIVO (n = 453)</th>
<th>IPI (n = 453)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo (95% CI)</td>
<td>NR (38.7–NR)</td>
<td>24.9 (16.6–35.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.68 (0.56–0.82)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

aStratified; bLog-rank test. NR, not yet reached.
Subgroup Analysis of RFS: **BRAF** Mutation Status

**BRAF Mutant**

<table>
<thead>
<tr>
<th></th>
<th>NIVO (n = 187)</th>
<th>IPI (n = 194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n</td>
<td>82</td>
<td>98</td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>NR (34.0–NR)</td>
<td>25.8 (15.9–NR)</td>
</tr>
<tr>
<td>HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.79 (0.59–1.06)</td>
<td></td>
</tr>
</tbody>
</table>

**BRAF Wild-type**

<table>
<thead>
<tr>
<th></th>
<th>NIVO (n = 197)</th>
<th>IPI (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n</td>
<td>79</td>
<td>117</td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>NR (38.7–NR)</td>
<td>16.8 (11.6–35.1)</td>
</tr>
<tr>
<td>HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.60 (0.45–0.80)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Unstratified.
EORTC 1325/KEYNOTE-54: Study Design

High-risk, resected, stage III cutaneous melanoma

Randomized 1:1
N=1019

PART 1: ADJUVANT THERAPY

Pembrolizumab 200 mg IV Q3W 1 year
Placebo IV Q3W 1 year
Total of 18 doses

PART 2: POST RECURRENT

Recurrence >6 months Recurrence Cross-over
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

The future of cancer therapy
Recurrence-Free Survival: subgroup analysis by AJCC-8

AJCC-8 Stage IIIA

- HR 0.76

AJCC-8 Stage IIIB

- HR 0.59

The future of cancer therapy

EORTC
Recurrence-Free Survival: subgroup analysis by AJCC-8 (cont)

AJCC-8 Stage III C

HR 0.48

AJCC-8 Stage III D

HR 0.69

The future of cancer therapy
Recurrence-Free Survival

BRAF V600E/K

HR 0.57

BRAF WT

HR 0.64

% alive and recurrence-free

Months

Patients at risk

Treatment arm | Total Event | HR (99% CI) | Stratified Logrank P-value

Pembrolizumab | 186 | 54 | 0.57 (0.37-0.89) | 0.0009

Placebo | 209 | 94 | Reference

Pembrolizumab | 233 | 69 | 0.64 (0.42-0.96) | 0.0039

Placebo | 214 | 97 | Reference

*Stratified by stage given at randomization

EORTC

The future of cancer therapy
Any other options?

Not in Europe
ECOG 1609 (NCT01274338) Ongoing Phase 3 Study

Pts with resectable IIIB, IIIC, M1a, M1b

N = approx. 1500

IPI High Dose 10 mg/kg Q3W x 4
then Q12W x 4 (1 year total)

High Dose IFN-α 2b (induction and maintenance: 1 year total)

IPI Low Dose 3 mg/kg IV Q3W x 4 then Q12W x 4 (1 year total)

Co-primary endpoints:
• OS
• RFS
Secondary endpoints
• QoL, biomarkers (RFS, OS)

Estimated primary completion date: May 2018

Study only powered to compare IFN with IPI, not IPI 3 vs 10 mg/kg.

First-step comparison of Ipi3 versus HDI: OS

ITT concurrently randomized cases (N=1051)

<table>
<thead>
<tr>
<th></th>
<th>Ipi3</th>
<th>HDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>130/523</td>
<td>134/528</td>
</tr>
<tr>
<td>HR (95.6% RCI)</td>
<td>0.78 (0.61, 0.99)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>5-year OS (95% CI)</td>
<td>0.72 (0.68, 0.76)</td>
<td>0.67 (0.62, 0.72)</td>
</tr>
</tbody>
</table>
First-step comparison of Ipi3 versus HDI: RFS

ITT concurrently randomized cases (N=1051)

<table>
<thead>
<tr>
<th></th>
<th>Ipi3</th>
<th>HDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>248/523</td>
<td>238/528</td>
</tr>
<tr>
<td>HR (99.4% CI)</td>
<td>0.85 (0.66, 1.09)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>4.5 years (2.6, -)</td>
<td>2.5 years (1.7, 3.3)</td>
</tr>
</tbody>
</table>

Probability

![Graph showing Kaplan-Meier curves for Ipi3 and HDI](image)
Second-step comparison of Ipilimumab (Ipi10) versus HDI: OS

ITT concurrently randomized cases (N=989)

<table>
<thead>
<tr>
<th></th>
<th>Ipi10</th>
<th>HDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>151/511</td>
<td>136/478</td>
</tr>
<tr>
<td>HR (95.6% RCI)</td>
<td>0.88 (0.69, 1.12)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>5-year OS (95% CI)</td>
<td>0.70 (0.65, 0.74)</td>
<td>0.65 (0.60, 0.70)</td>
</tr>
</tbody>
</table>
Second-step comparison of Ipi10 versus HDI: RFS

ITT concurrently randomized cases (N=989)

<table>
<thead>
<tr>
<th></th>
<th>Ipi10</th>
<th>HDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>249/511</td>
<td>228/478</td>
</tr>
<tr>
<td>HR (99.4% CI)</td>
<td>0.84 (0.65, 1.09)</td>
<td>NS</td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>3.9 years (2.9, -)</td>
<td>2.4 years (1.6, 3.0)</td>
</tr>
</tbody>
</table>
Study of Nivolumab Combined With Ipilimumab Compared With Nivolumab Alone After Complete Surgical Removal of Stage IIIB/C/D or IV Melanoma (CheckMate 915/CA209-915/NCT03068455)

- **Purpose**
  - To determine if NIVO+IPI is more effective than NIVO alone in delaying recurrence in patients with complete resection of stage IIIB/C/D or stage IV melanoma

- **Primary endpoint**
  - RFS measured by time, approximately 30 months

- **Secondary endpoints**
  - OS measured by time, up to 5 years
  - PD-L1 expression measured by immunoassay, approximately 3 years

- **Study-specific eligibility criteria**
  - 12 years and older
  - Completely resected stage IIIB/C/D or IV melanoma within 12 weeks of study
  - Patients must be active or, if limited, be able to carry out daily activities
  - No prior anticancer treatment for melanoma (except surgery and/or adjuvant radiation therapy after CNS lesion resection)
  - No history of uveal melanoma
  - No active or known autoimmune disease

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CNS = central nervous system; IPI = ipilimumab; IV = intravenous; NIVO = nivolumab; OS = overall survival; PD-L1 = programmed death ligand-1; RFS = recurrence-free survival

• The study remains double-blinded and will continue to assess the other co-primary endpoint of RFS in the all-comer (intent-to-treat) population.
• The trial randomized 1,943 patients to receive either Opdivo 240 mg intravenously every two weeks and Yervoy 1 mg/kg every six weeks or Opdivo 480 mg every four weeks for one year.
In patients with very-low-risk stage IIIA disease (non-ulcerated primary ≤2 mm thickness, SLN metastasis <1 mm), the toxicity of adjuvant therapy may outweigh the benefit.

Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported.

Adjuvant dabrafenib/trametinib and pembrolizumab are category 1 options for patients with AJCC 7th Edition stage IIIA with SLN metastasis >1 mm or stage IIIB/C disease. Adjuvant nivolumab is a category 1 option for patients with AJCC 7th Edition stage IIIB/C disease.

Randomized clinical trials testing adjuvant anti-PD-1 therapy included patients with sentinel node-positive disease at higher risk of recurrence: those with ulcerated primary (nivolumab, pembrolizumab) or an SLN metastasis >1 mm (pembrolizumab).

In patients with a positive sentinel node, two prospective randomized phase III studies have demonstrated no improvement in melanoma-specific survival or OS in patients undergoing CLND compared to those who underwent nodal basin US surveillance, although only one study (MSLT-II) included primary melanomas on the head and neck. CLND did provide additional prognostic information as well as improvement in regional control/recurrence at the expense of increased morbidity, including wound complications and long-term lymphedema. Factors that predict non-SLN positivity include sentinel node tumor burden, number of positive nodes, and thickness/ulceration of the primary tumor. Nodal basin US surveillance may not be preferred over therapeutic lymph node dissection in all cases (eg, patient preference due to the logistics of surveillance).

CLND was required for the frequency of clinical exam and US surveillance to be consistent with the two prospective randomized trials (MSLT-II and DeCOG): at least every 4 months during the first 2 years, then every 6 months during years 3 through 5. The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.

The randomized clinical trial testing adjuvant dabrafenib/trametinib combination therapy for patients with BRAF V600E/K mutation included patients with sentinel node-positive disease at higher risk of recurrence: those with ulcerated primary and/or SLN metastasis >1 mm.

In the event of unacceptable toxicities to dabrafenib/trametinib, other BRAF/MEK inhibitor combinations can be considered.
<table>
<thead>
<tr>
<th>CLINICAL/PATHOLOGIC STAGE</th>
<th>WORKUP</th>
<th>PRIMARY TREATMENT</th>
<th>ADJUVANT TREATMENT</th>
</tr>
</thead>
</table>
| Stage III (clinically positive node[s]) | Core biopsy or FNA preferred if feasible. If needle biopsy is not possible, incisional or excisional biopsy is acceptable. Imaging for baseline staging and to evaluate specific signs or symptoms. BRAF mutation testing. | Wide excision of primary tumor (category 1) + therapeutic lymph node dissection (TLND). | Systemic therapy options:  
- Preferred regimens:  
  - Nivolumab (category 1)  
  - Pembrolizumab (category 1)  
  - Dabrafenib/trametinib for patients with BRAF V600-activating mutation (category 1) and/or  
  - Locoregional therapy option:  
    - Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, gross and/or histologic extracapsular extension (category 2B) or Observation.  

| See Follow-up (ME-9) |

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1 See Principles of Imaging—Workup (ME-D).
2 See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-E).
3 See Principles of Molecular Testing (ME-C).

The choice of adjuvant systemic treatment versus observation should take into consideration the patient’s risk of melanoma recurrence and the risk of treatment toxicity.

Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported.

In the event of unacceptable toxicities to dabrafenib/trametinib, other BRAF/MEK inhibitor combinations can be considered.

In patients with extensive resectable nodal disease at very high risk of recurrence after complete resection, or if resectability of nodal disease is uncertain, recommend multidisciplinary tumor board review to consider neoadjuvant systemic therapy preferably in the context of a clinical trial. For patients with unresectable nodal disease, consider treatment with systemic therapy (options shown on ME-I) followed by resection, or treat as stage IV (ME-15).

Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in RFS or OS. Its benefits must be weighed against potential toxicities such as lymphedema (limb) or oropharyngeal complications. The impact of these potential toxicities should be considered in the context of available systemic adjuvant treatment options.

See Principles of Radiation Therapy for Melanoma (ME-H).

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Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
The data currently available establish both PD-1 blockade and dabrafenib/trametinib as recommended adjuvant treatments options for stage IIIA (SN >1 mm), B and C for BRAFmutated melanoma. Some of the current approval include all stage III, regardless of SN deposit. Decision of treatment for stage IIIA SN<1mm should be made on an individual basis, considering the exact prognosis of the patient. This decision process will be discussed in detail in the upcoming ‘ESMO Consensus Conference Recommendations on Melanoma’ publication.

In BRAF WT patients, PD-1 blockade is the only recommended option.

For BRAF mutated melanoma, as there is no direct efficacy comparison between dabrafenib/trametinib versus PD-1 blockade, individual treatment decision should be made with the patients, factoring in the toxicity profiles.
Unanswered questions

• Low risk stage IIIA (tumour burden in SLN<1mm)
• BRAF positive patients – no data
• Long term toxicity
• Survival data
All patients pN0: T2-T4 patients are included only if SLN negative, patients with T1N0 melanoma are included regardless of whether SLN biopsy was performed.
Completely Resected Stage IIB/C melanoma w/ standard WLE and negative SLN biopsy
N = 1000
Stratify by T Stage
Randomize 2:1
NIVO IV 480 mg Q4W 12 mo
N = 667
Placebo IV Q4W 12 mo
N = 333
In treatment or Follow-up
In the event of recurrence
Blinded Nivolumab/Placebo Treatment
Optional on-protocol open-label Nivo treatment after 1st recurrence

Treat per Investigator choice
If participant:
• Not eligible for Open-Label Nivo
• Decline Open-Label Nivo

Pediatric dosing weight-based under 40 kg and for sites preferring weight-based dosing in pediatrics

Tumor material obtained from surgery or biopsy
Recurrence > 6 months after completion of 1 year nivolumab treatment
After recurrence, patient assigned to placebo arm will be offered to crossover to nivolumab
Resectable disease (Arm 1): Nivo 480 mg IV Q4W for 12 mo
Unresectable disease (Arm 2): Nivo 480 mg IV Q4W for 24 mo
Special Thanks to my Investigator Team: 238 (20 enrolled), 915 (43 enrolled), Trilogy (20 enrolled), 265 (33 enrolled), Imspire 170 (19 enrolled), Combi-I (9 enrolled), and ImmunoCobi (30 enrolled)
My research cat
Thank you