AGGIORNAMENTI E NOVITÀ NEL TRATTAMENTO DEL MELANOMA

Dr Paolo Pochettino
Ospedale Gradenigo
Torino
Unprecedented Progress in Treatment of Melanoma

1 year survival

Achieved by clinical trials

30-35%
Ipilimumab
Ipilimumab
Vemurafenib
Dabrafenib

46% 47% 56% 70%

80% Dab + Tram
85% Nivo + Ipi
63% Nivo
69% Pembrolizumab

New results
Pembro vs Ipi
PD-1 + Ipi

Slide courtesy G V Long
AGGIORNAMENTO
STUDI CLINICI
IMMUNOTERAPIA
What do we know about new immunotherapies in melanoma?

1. Ipilimumab: 15-20% response rate
2. PD-1 antibodies: 30-40% response rate
3. Durable responses—and Complete Resp
4. PD-1 antibodies “better” than ipilimumab
5. Fewer immune adverse events with PD-1 antibodies compared to ipilimumab
6. Combination PD-1 and ipilimumab higher response rate compared to ipilimumab alone
KEYNOTE-006: International, Randomized, Phase III Study

Patients
- Unresectable, stage III or IV melanoma
- ≤1 prior therapy, excluding anti-CTLA-4, PD-1, or PD-L1 agents
- Known *BRAF* status
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease

Stratification factors:
- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive vs negative)

R 1:1:1

Pembrolizumab
10 mg/kg IV Q2W

Pembrolizumab
10 mg/kg IV Q3W

Ipilimumab
3 mg/kg IV Q3W x 4 doses

Primary end points: PFS and OS
Secondary end points: ORR, duration of response, safety
OS at the Second Interim Analysis

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 12 mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab Q2W</td>
<td>NR (NR-NR)</td>
<td>74.1%</td>
<td>0.63 (0.47-0.83)</td>
<td>0.00052</td>
</tr>
<tr>
<td>Pembrolizumab Q3W</td>
<td>NR (NR-NR)</td>
<td>68.4%</td>
<td>0.69 (0.52-0.90)</td>
<td>0.00358</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>NR (12.7-NR)</td>
<td>58.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time, months

Analysis cut-off date: March 3, 2015.

NEJM, Robert et al 2015
Clinical Response, PFS and Safety in Patients With Advanced Melanoma Receiving Nivolumab Combined with Ipilimumab versus Ipilimumab Monotherapy in CheckMate 069 Study


1Dana-Farber Cancer Institute, Boston, MA, USA; 2Ludwig Center at Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3University of Louisville, Louisville, KY, USA; 4New York University, New York, NY, USA; 5Gustave Roussy and INSERM U981, Villejuif-Paris-Sud, France; 6Huntsman Cancer Institute, Salt Lake City, UT, USA; 7Beth Israel Deaconess Medical Center, Boston, MA, USA; 8Washington University, St. Louis, MO, USA; 9Institut Universitaire du Cancer, Toulouse, France; 10Greenville Health System, Greenville, SC, USA; 11St Luke’s Cancer Center and Temple University, Bethlehem, PA, USA; 12University of New Mexico, Albuquerque, NM, USA; 13Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; 14California Pacific Center for Melanoma Research, San Francisco, CA, USA; 15Duke University, Durham, NC, USA; 16Oregon Health & Science University, Portland, OR, USA; 17Bristol-Myers Squibb, Princeton, NJ, USA; 18Bristol-Myers Squibb, Wallingford, CT, USA
Introduction

• Ipilimumab (IPI; anti-CTLA-4)
  – Improved OS when administered as monotherapy in previously-treated patients\(^1\)

• Nivolumab (NIVO; anti-PD-1)
  – Improved OS versus DTIC in patients with BRAF wild-type, previously untreated, advanced melanoma in a phase III study\(^2\)

• Combination of NIVO and IPI
  – Demonstrated high ORR, durable response, and 2–year OS rate of up to 88% in a phase I melanoma study\(^3,4\)
  – Recently shown to improve ORR and PFS in the phase II melanoma study CA209-069\(^5\)

• Study CA209-069: analysis of ORR, PFS, and safety in all randomized patients and in predefined subgroups, including those with poor prognostic factors

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CTLA-4 = cytotoxic T-lymphocyte antigen-4; DTIC = dacarbazine; ORR = overall response rate; OS = overall survival; PD-1 = programmed death-1; PFS = progression-free survival
Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL)

Mario Sznol,1 Harriet Kluger,1 Margaret K. Callahan,2 Michael A. Postow,2 RuthAnn Gordon,2 Neil H. Segal,2 Naiyer A. Rizvi,2 Alexander M. Lesokhin,2 Michael B. Atkins,3 John M. Kirkwood,4 Matthew M. Burke,1 Amanda Ralabate,1 Angel Rivera,1 Stephanie A. Kronenberg,2 Blessing U. Agunwamba,2 William Feely,5 Quan Hong,5 Suba Krishnan,5 Jedd D. Wolchok2

1Yale University School of Medicine and Yale Cancer Center, New Haven, CT, USA; 2Memorial Sloan-Kettering Cancer Center, New York, NY, USA; 3Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA; 4University of Pittsburgh Medical Center, Pittsburgh, PA, USA; 5Bristol-Myers Squibb, Princeton, NJ, USA

PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.
Overall Survival for Concurrent Therapy by Dose Cohort

- 2 Yr OS 88%
- 2 Yr OS 79%
- 2 Yr OS 50%

Pts at Risk:
- Nivo 0.3 mg/kg + IPI 3 mg/kg
- Nivo 1 mg/kg + IPI 3 mg/kg
- Nivo 3 mg/kg + IPI 1 mg/kg
- Nivo 3 mg/kg + IPI 3 mg/kg
- Concurrent Cohort

 Timeline: 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48 months
Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

Michael A. Postow, M.D., Jason Chesney, M.D., Ph.D., Anna C. Pavlick, D.O., Caroline Robert, M.D., Ph.D., Kenneth Grossmann, M.D., Ph.D., David McDermott, M.D., Gerald P. Linette, M.D., Ph.D., Nicolas Meyer, M.D., Jeffrey K. Giguere, M.D., Sanjiv S. Agarwala, M.D., Montaser Shaheen, M.D., Marc S. Ernstoff, M.D., David Minor, M.D., April K. Salama, M.D., Matthew Taylor, M.D., Patrick A. Ott, M.D., Ph.D., Linda M. Rollin, Ph.D., Christine Horak, Ph.D., Paul Gagnier, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and F. Stephen Hodi, M.D.
Phase II CA209-069: Study Design

Eligible patients with unresectable stage III or IV melanoma
- Treatment-naïve
- BRAF WT (N = 100) or MT (N = 50)
- Stratified by BRAF status

NIVO 1 mg/kg + IPI 3 mg/kg
Q3Wx4
Double-blind

NIVO 3 mg/kg
Q2W

Treat until: disease progression\(^a\) or unacceptable toxicity

Placebo + IPI 3 mg/kg
Q3Wx4

Placebo
Q2W

Primary endpoint:
- ORR in BRAF WT patients

Secondary endpoints:
- PFS in BRAF WT patients
- ORR and PFS in BRAF MT patients
- Safety

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\(^a\)Treatment beyond initial investigator-assessed RECIST v1.1-defined progression is permitted in patients experiencing clinical benefit and tolerating study therapy. IPI patients have an option to receive nivolumab monotherapy after progression. Upon confirmed progression and change of treatment, all patients are unblinded.

MT = mutation; PFS = progression-free survival; Q3W = every 3 weeks; WT = wild type
### Objective Response, Investigator-Assessed

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

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

<sup>b</sup>RECIST v1.1

Cl = confidence interval
Time to and Durability of Response (All Randomized Responders)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N = 95)</th>
<th>IPI (N = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to response, months (range)</td>
<td>2.8 (2.3, 9.9)</td>
<td>2.7 (2.5, 7.9)</td>
</tr>
<tr>
<td>Median duration of response, months (range)</td>
<td>NR (0–12.1)b</td>
<td>NR (3.5–9.8)b</td>
</tr>
<tr>
<td>Ongoing response among responders, n (%)</td>
<td>46/56 (82)</td>
<td>4/5 (80)</td>
</tr>
</tbody>
</table>

a Minimum follow-up of 11 months from date of randomization
b Censored data (response ongoing)
NR = not reached

- 68% of patients (30/44) who discontinued the NIVO + IPI combination due to drug-related toxicity experienced a complete or partial response
PFS in All Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=95)</th>
<th>IPI (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or disease progression, n/N</td>
<td>42/95</td>
<td>32/47</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR</td>
<td>3.0 (2.8–5.1)</td>
</tr>
<tr>
<td>HR (95% CI), p-value</td>
<td>0.39 (0.25–0.63), p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
## Safety Summary

<table>
<thead>
<tr>
<th>Patients reporting event, % (n/N)</th>
<th>NIVO + IPI&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IPI&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>91 (86/94)</td>
<td>54 (51/94)</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>90 (43/48)</td>
<td>54 (26/48)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>94 (43/46)</td>
<td>52 (24/46)</td>
</tr>
<tr>
<td>M1c disease</td>
<td>89 (39/44)</td>
<td>59 (26/44)</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation</td>
<td>47 (44/94)</td>
<td>38 (36/94)</td>
</tr>
<tr>
<td>Treatment-related death</td>
<td>3 (3/94)</td>
<td>0 (0/46)</td>
</tr>
</tbody>
</table>

*Safety was evaluated in all patients who received at least one dose of study treatment.

- Summary of treatment-related deaths (n=3)
  - History of cardiac issues; death due to ventricular arrhythmia, 29 days after last treatment
  - Sudden death 69 days after last treatment, while patient was clinically improving from pneumonitis/iatrogenic pneumothorax
  - Sudden death 3 days after resolution of grade 3 pneumonia and grade 4 hypercalcemia, 87 days after last treatment. Patient cause of death was later defined as panhypopituitarism with severe cortisol deficiency and adrenal crisis leading to death
### Most Common Treatment-Related Select AEs

<table>
<thead>
<tr>
<th>Patients reporting event, %</th>
<th>NIVO + IPI (N = 94)</th>
<th>IPI (N = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Skin AEs</td>
<td>71</td>
<td>10</td>
</tr>
<tr>
<td>Rash</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal AEs</td>
<td>51</td>
<td>21</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>11</td>
</tr>
<tr>
<td>Colitis</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Endocrine AEs</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic AEs</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>ALT increased</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>AST increased</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary AEs</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Renal AEs</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

- Select adverse events were defined as those with a potential immunologic etiology

ALT = alanine aminotransferase; AST = aspartate aminotransferase

**SLIDES ARE THE PROPERTY OF THE AUTHOR, PERMISSION REQUIRED FOR REUSE.**
Conclusions

• Compared with IPI alone, the NIVO + IPI combination significantly improved ORR and PFS in all randomized patients
  – NIVO + IPI ORR (59%; CR: 22%) versus IPI ORR (11%; CR: 0%)
  – ORR and PFS benefit was observed irrespective of BRAF status, tumor PD-L1 status, and presence of poor prognostic factors
• Treatment-related AEs were reported more frequently with NIVO + IPI than with IPI alone
• Patients with poor prognostic factors had a similar safety profile to the entire population
• AEs were generally managed using established guidelines and the majority of grade 3/4 AEs resolved with the use of IMM at a median of 5 weeks
• The NIVO + IPI combination provided a favorable benefit-risk profile in treatment-naïve advanced melanoma patients, including those with poor prognostic factors
TARGET THERAPY
Update of Progression-Free Survival and Correlative Biomarker Analysis From coBRIM: Phase 3 Study of Cobimetinib Plus Vemurafenib in Advanced BRAF-Mutated Melanoma

James Larkin, Yibing Yan, Grant McArthur, Paolo Ascierto, Gabriella Liszkay, Michele Maio, Mario Mandalà, Lev Demidov, Daniil Stoyakovskiy, Luc Thomas, Luis de la Cruz-Merino, Victoria Atkinson, Caroline Dutriaux, Claus Garbe, Matthew Wongchenko, Isabelle Rooney, Ilsung Chang, Stephen P. Hack, Brigitte Dréno, Antoni Ribas
Background

- The most common mechanism of acquired resistance to vemurafenib monotherapy in \(BRAF^{V600}\)-mutated melanoma is MAPK reactivation through MEK\(^1,2\).

- In the coBRIM study, addition of the MEK inhibitor cobimetinib to vemurafenib resulted in a clinically relevant and statistically significant treatment benefit after 7.3 months follow-up\(^3\):
  - Median PFS 9.9 months vs. 6.2 months (HR 0.51; 95% CI, 0.39 to 0.68; \(P<0.0001\))
  - Overall response rate 68% vs. 45% (\(P<0.0001\))
  - Complete response rate 10% vs. 4%

- Updated PFS and response rate data are presented after longer follow-up (14.2 months).

- \(BRAF^{V600}\)-mutated melanomas may harbor additional oncogenic mutations

- Data on the coexisting oncogenic mutations in pretreatment tumor samples and the treatment outcomes of patients with these mutations are presented.

coBRIM Study Design

- Melanoma, unresectable locally advanced or metastatic (n = 495)
- BRAF\textsuperscript{V600} 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\textsuperscript{1}

Secondary end points
OS, objective response rate, duration of response, PFS, IRC assessed, safety, pharmacokinetics, quality of life: QLQ-C30 and EQ-5D

Primary analysis for PFS:
Performed in 2014 with the data cutoff as May 9, 2014. Protocol-specified first OS interim analysis was also performed\textsuperscript{1}

Updated analysis for PFS:
Presented here with the data cutoff as January 16, 2015.

BID, twice daily; ECOG, Eastern Cooperative Oncology Group; EO, EuroQol; HR, hazard ratio; IRC, independent review committee; OS, overall survival; PFS, performance status; QD, once daily; QOL, quality-of-life questionnaire.

coBRIM Updated Investigator-Assessed PFS

Kaplan-Meier Plot for PFS
Intent-to-Treat Population

Survival Distribution Function (%)
100
80
60
40
20
0

No. of patients at risk
Vemurafenib + cobimetinib
238 215 190 168 142 118 79 46 21 8 1
Vemurafenib + placebo
240 205 150 115 87 67 45 30 17 3

Stratified HR:
The median PFS was 5.2 months in Pbo + Vem, and 9.9 months in Cobi + Vem (HR, 0.51; 95% CI, 0.39-0.68) at the May 9, 2014 data cutoff. 

Data cutoff of January 16, 2015 was 1 year from enrollment of last patient.
coBRIM Updated Best Objective Response Rate and Duration of Response

<table>
<thead>
<tr>
<th></th>
<th>Cobimetinib + Vemurafenib n = 247</th>
<th>Placebo + Vemurafenib n = 248</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR), n (%)</td>
<td>39 (15.8)</td>
<td>26 (10.5)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>133 (53.8)</td>
<td>98 (39.5)</td>
</tr>
<tr>
<td>Objective response rate (ORR), n (%)</td>
<td>172 (69.6) (95% CI, 63.49-75.31)</td>
<td>124 (50.0) (95% CI, 43.61-56.39)</td>
</tr>
<tr>
<td>Difference in ORR, %</td>
<td>19.64a (95% CI, 10.95-28.32)</td>
<td></td>
</tr>
<tr>
<td>Duration of response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with event, n (%)</td>
<td>84 (48.8)</td>
<td>73 (58.9)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>12.98 (11.10-16.62)</td>
<td>9.23 (7.52-12.78)</td>
</tr>
<tr>
<td>Range</td>
<td>2.86-20.11</td>
<td>1.77-17.68</td>
</tr>
</tbody>
</table>

*aAt the primary analysis ORR was 68% and 45%, respectively, and CR was 10% and 4%, respectively. Larkin J et al. N Engl J Med. 2014;371:1867-1876. Data cutoff was January 16, 2015.
coBRIM Update: Summary and Conclusions

• Updated coBRIM efficacy data with median follow-up of 14.2 months confirmed the clear and definitive clinical benefit of adding cobimetinib to vemurafenib in $BRAF^{V600}$ mutated melanoma
  – Median PFS in excess of 12 months
  – 12.25 months for cobimetinib + vemurafenib and 7.2 months for placebo + vemurafenib (HR 0.58; 95% CI, 0.46-0.72)
  – ORR 69.6% for cobimetinib + vemurafenib and 50% for placebo + vemurafenib

• A fraction of $BRAF^{V600}$ mutated melanoma patients (11%) were identified to have co-existing baseline RAS/RAF/RTK tumor mutations

• Co-existing baseline RAS/RAF/RTK mutations did not appear to affect PFS or ORR in patients treated on the coBRIM study

• The coBRIM study continues to follow patients for OS. The final OS analysis is expected around the end of 2015
PROSPETTIVE FUTURE
S1320 A Randomized Phase II Trial of Intermittent versus Continuous Dosing Of Dabrafenib and Trametinib in BRAF<sup>V600E/K</sup> Mutant Melanoma. (A. Algazi, PI)

Features:
- 10 week lead-in
- 3 week holiday / 5 weeks on treatment
- q8 week assessments

<table>
<thead>
<tr>
<th></th>
<th>H&lt;sub&gt;0&lt;/sub&gt;</th>
<th>H&lt;sub&gt;1&lt;/sub&gt;</th>
<th>HR</th>
<th>2-sided α</th>
<th>Power</th>
<th>Patients registered</th>
<th>Patients eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>9.4 months</td>
<td>14.1 months</td>
<td>0.67</td>
<td>20%</td>
<td>90%</td>
<td>280</td>
<td>226</td>
</tr>
</tbody>
</table>

Rationale for 3 week treatment holiday

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effective t&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>Model Level within 2 wks</th>
<th>Anticipated Target Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib</td>
<td>8 hours</td>
<td>Undetectable</td>
<td>Subtherapeutic</td>
</tr>
<tr>
<td>Dabrafenib metabolites</td>
<td>9.7 – 22.2 hours</td>
<td>Undetectable</td>
<td>Subtherapeutic</td>
</tr>
<tr>
<td>Trametinib</td>
<td>4 days</td>
<td>Detectable</td>
<td>Subtherapeutic after 11 days</td>
</tr>
</tbody>
</table>

Based on GSK modeling data  Slide Courtesy of Ribas
Next Steps Immunotherapy

Building on the Backbone

Monotherapy vs Doublet Therapy
PD-1 alone or PD-1 and Ipi

Triple Therapy?

+ 

Vaccine Strategies
Other immunotherapies
GM-CSF
IDO inhibitors
OX40
LAG 3

Radiation: RadVax
Anti-VEGF