MELANOMA Changing Landscape

Alexander Eggermont

2013
Dublin Melanoma Conference
ACTIVITY IN STAGE IV MELANOMA

Change in target lesions from baseline (%)

Patients
THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION
Frequency distribution of genetic alterations in BRAF, NRAS, and KIT among four groups of melanoma

**BRAF Rate by Decade**

- >90% V600E
- >25% V600K/D/R

Menzies AM et al, ASCO 2011, Melanoma Oral Session, Abs# 8507
Jakob JA et al J Clin Oncol 29:526s, 2011 (suppl 15s; abstr 8500)
Cheng S et al J Clin Oncol 29:549s, 2011 (suppl 15s; abstr 8597)
Rubinstein JC et al J Transl Med 8:67, 2010
BRAF and NRAS-mutant melanomas

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median OS (y)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>94</td>
<td>1.3</td>
<td>------</td>
</tr>
<tr>
<td>BRAF with inhibitor</td>
<td>41</td>
<td>NR</td>
<td>.02</td>
</tr>
<tr>
<td>BRAF without inhibitor</td>
<td>112</td>
<td>0.9</td>
<td>.10</td>
</tr>
<tr>
<td>NRAS</td>
<td>66</td>
<td>0.7</td>
<td>.003</td>
</tr>
</tbody>
</table>

Inhibitors: PLX-4032; GSK-2118436; GSK-1120212; AZD-6244
Molecular Alterations in Melanoma

- **FGFR**
- **PTEN**
- **PI3K**
- **Akt**
- **GRB2**
- **SOS**
- **Ras GDP**
- **N-Ras GTP**
- **C-Raf**
- **MEK**
- **ERK**
- **MITF**
- **TOR**
- **CDK2/4**
- **Cyclin D**
- **p16**
- **acral and mucosal melanoma**
- **15% mutation**
- **50%-65% V600E mutation**
- **25%-50% loss**
- **Frequent loss**
- **Amplified or mutated in 20%-40%**
- **Amplified in 10%-15%**
- **Amplified in 10%**
- **Amplified in 30%**
- **Amplified in 30%**

PFS 1.6-5.5 mts  
Gain: 3.9 mts  
HR 0.26

OS 9.6-13.2 mts  
Gain 3.6 mts*  
HR 0.62
DABRAFENIB: Primary Endpoint: PFS
Investigator-Assessed (Cut-off: 19 December 2011)

Hazard ratio 0.30 (95% CI: 0.18, 0.51); p<0.0001

Dabrafenib:
median PFS 5.1 mos

DTIC:
median PFS 2.7 mos

On randomized study treatment at cut-off: dabrafenib 57%, DTIC 27%
Median follow-up time: 4.9 months (dabrafenib 5.1 mos, DTIC 4.8 mos.)
Overall survival (Feb 01, 2012 cutoff)
Censored at crossover

Vemurafenib (N=337)
- Median f/u 12.5 mos.

Dacarbazine (N=338)
- Median f/u 9.5 mos.

Hazard ratio 0.70
(95% CI: 0.57 - 0.87)
p<0.001 (post-hoc)

No. at risk:
- Dacarbazine: 338 244 173 111 79 50 24 4 0
- Vemurafenib: 337 326 280 231 178 109 44 7 1

Chapman et al ASCO 2012
### Selected adverse events (% of patients)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Vemurafenib, n= 337</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>56</td>
<td>6</td>
</tr>
<tr>
<td>Rash</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>↑LFTs</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Cutaneous SCC</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>–</td>
</tr>
</tbody>
</table>

Discontinuations due to AE: 7% Vemurafenib; 2% Dacarbazine

Data-cut: Feb 01, 2012

8 patients reported primary melanoma in the vemurafenib group.
Squamous Cell Carcinoma (Skin)

Thigh: Week 6

- Histopathology: Low-grade squamous cell carcinoma
- In 20-25% of patients
- Induced in first 4 months (?)

SCC: Time to Event < 12-14 weeks

= individual pt event
= second event

Kefford et al, Sydney 2010
## Vemurafenib-associated skin manifestations (1)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>36-53%</td>
<td>Maculopapular Keratosis pilaris</td>
</tr>
<tr>
<td></td>
<td>Grade 3: 6-8%</td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>30</td>
<td>UVA-induced</td>
</tr>
<tr>
<td>HFSR hyperkeratosis</td>
<td>20</td>
<td>Rubbing, pressure areas</td>
</tr>
<tr>
<td>Hair modification Alopecia</td>
<td>100-8</td>
<td>Can be reversible</td>
</tr>
</tbody>
</table>
### Vemurafenib-associated skin manifestations (2)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic lesions</td>
<td>?</td>
<td>Multiple, face</td>
</tr>
<tr>
<td>Papillomas Warts</td>
<td>20-50</td>
<td>Multiple</td>
</tr>
<tr>
<td>Keratoacanthomas SCC</td>
<td>20-30</td>
<td>Multiple</td>
</tr>
<tr>
<td>Eruptive navi Melanomas</td>
<td>?</td>
<td>Median time to occurrence 6-8 wks</td>
</tr>
</tbody>
</table>
INDUCTION NEW MELANOMAS under Vemurafenib

Atypical Melanocytic Proliferations and New Primary Melanomas in Patients With Advanced Melanoma Undergoing Selective BRAF Inhibition

Lisa Zimmer, Uwe Hillen, Elisabeth Livingstone, Mario E. Lacouture, Klaus Busam, Richard D. Carvajal, Friederike Egberts, Axel Hauschild, Mohammed Kashani-Sabet, Simone M. Goldinger, Reinhard Dummer, Georgina V. Long, Grant McArthur, André Scherag, Antje Sucker, and Dirk Schadendorf

ABSTRACT

Purpose
Selective inhibition of mutant BRAF by using class I RAF inhibitors in patients with metastatic melanoma has resulted in impressive clinical activity. However, there is also evidence that RAF inhibitors might induce carcinogenesis or promote tumor progression via stimulation of MAPK signaling in RAF wild-type cells. We analyzed melanocytic lesions arising under class I RAF inhibitor treatment for dignity, specific genetic mutations, or expression of signal transduction molecules.

Patients and Methods
In all, 22 cutaneous melanocytic lesions that had either developed or considerably changed in morphology in 19 patients undergoing treatment with selective BRAF inhibitors for BRAF-mutant metastatic melanoma at seven international melanoma centers within clinical trials in 2010 and 2011 were analyzed for mutations in BRAF and NRAS genes and immunohistologically assessed for expression of various signal transduction molecules in comparison with 22 common nevi of 21 patients with no history of BRAF inhibitor treatment.

Results
Twelve newly detected primary melanomas were confirmed in 11 patients within 27 weeks of selective BRAF blockade. In addition, 10 nevi developed of which nine were dysplastic. All melanocytic lesions were BRAF wild type. Explorations revealed that expression of cyclin D1 and pAKT was increased in newly developed primary melanomas compared with nevi (P = .01 and P = .03, respectively). There was no NRAS mutation in common nevi, but BRAF mutations were frequent.

Conclusion
Malignant melanocytic tumors might develop with increased frequency in patients treated with selective BRAF inhibitors supporting a mechanism of BRAF therapy-induced growth and tumorigenesis. Careful surveillance of melanocytic lesions in patients receiving class I RAF inhibitors seems warranted.

J Clin Oncol 30:2375-2383. © 2012 by American Society of Clinical Oncology
IMPLICATIONS FOR ADJUVANT SETTING

- Short impact on OS in stage IV
  → PD in stage IV mostly new lesions while on treatment?

- TOXICITY IS MAJOR DETERMINANT IN ADJUVANT SETTING

- RISKS
  → SCC, New Melanomas
  → Colon Polyps
  → Gastric Polyps
  → Pancreas ????

- Against use of BRAFinhibitors alone in adjuvant setting
  → Problems solved by BRAFinh + MEKinh ?
SUCCESS AND FAILURE
Multiple Mechanisms of Preexisting or Acquired Resistance to BRAF Inhibitors Identified

LETTER

Melanomas acquire resistance to B–RAF(V600E) inhibition by RTK or N–RAS upregulation

Ramin Nazarian,²,³, Huihui Shi,²,³, Qi Wang,²,³, Xiaojia Kang,²,³, Richard C. Korge,²,³, Hae Se Lee,⁴, Zugen Chen⁴, Mi-Kyung Lee⁴, Narys Attar,²,³, Woosam Son,⁴,⁵, Hume decking,²,³, Stanley F. Nelson⁴,⁵, Grant McArthur,²,⁵, Jeffrey A. Sosman,²,³, Antoni Ribas²,³ & Roger S. Lo⁴,⁵

LETTER

COT drives resistance to RAF inhibition through MAP kinase pathway reactivation

Gary M. Johannessen²,³, Jesse S. Boeheim⁴, So Young Kim²,³,⁴, Sagara R. Thomas⁴, Leslie Wardwell⁴, Laura A. Joho²,³, Caroline M. Emery⁴, Nikolas Stramati⁴, Alexandria P. Coq⁴, Jordi Barretina²,³, Giordano Capogrossi⁴, Harley Hiebert⁴,⁵, Kwan H. Murray²,³, Koochak Talebi-Adradzhi²,³,⁴,⁵, David B. Hill⁴,⁵, Marc Veled⁴,⁵, Janet B. Drex⁴,③,④,⑤, Kyoung-Yong Kang⁴,③,④,⑤, Oian Allens⁴,③,④,⑤, Jennifer L. Harris⁴,③,④,⑤, Christopher J. Wilson⁴,③,④,⑤, Vj B. Myer⁴,③,④,⑤, Peter M. Finnin⁴,③,④,⑤, David E. Bred⁴,③,④,⑤, Thomas M. Roberts⁴,③,④,⑤, Todd Golub⁴,③,④,⑤, Keith F. Flaherty⁴,③,④,⑤, Kermitl Dummer⁴,③,④,⑤, Barbara L. Weber⁴,③,④,⑤, William R. Sellers⁴,③,④,⑤, Robert Schaver⁴,③,④,⑤, Jennifer A. Wang⁴,③,④,⑤, William G. Fishman⁴,③,④,⑤ & Levi A. Knisley⁴,③,④,⑤


- PDGFRβ overexpression: 4/11 biopsies from relapsed patients¹
- NRAS mutations (Q61K or R): 2/15 samples¹
- Elevated COT expression which reactivated ERK signaling: 2/3 samples²
- Increased levels of IGF-1R and pAKT: activated PI3K pathway signaling (1/5)³
- Acquired a MEK mutation at C121S which reactivates the ERK signaling (1/1)⁴
Molecular Alterations in Melanoma

**MEK Inhibitors (ASCO 2012)**

- **FGFR**
- **PTEN**
- **PI3K**
- **Akt**
- **GRB2**
- **SOS**
- **Ras GDP**
- **N-Ras GTP**
- **C-Raf**
- **B-Raf**
- **MEK**
- **ERK**
- **CDK2/4**
- **Cyclin D**
- **p16**
- **MITF**
- **TOR**
- **Acral and mucosal melanoma**
- **V600E mutation**

- Amplified or mutated in 20%-40%
- 15% mutation
- 50%-65% V600E mutation
- Amplified in 10%-15%
- 25%-50% loss
- Frequent loss
- Amplified in 30%

**MEK Inhibitor TRAMETINIB vs DTIC**

**METRIC PFS**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Median (months)</th>
<th>HR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trametinib</td>
<td>96 (54)</td>
<td>4.8</td>
<td>0.44 (0.31, 0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>68 (72)</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Robert et al ASCO 2012
Molecular Alterations in Melanoma

BRAF + MEK Inhibitors (ASCO 2012)

- **FGFR**
- **PTEN**
- **PI3K**
- **Akt**
- **TOR**
- **KIT**
- **GRB2**
- **SOS**
- **Ras GDP**
- **N-Ras GTP**
- **C-Raf**
- **MEK**
- **ERK**
- **ELK**
- **MITF**
- **CDK2/4**
- **Cyclin D**
- **p16**

- **Amplified or mutated in 20%-40% acral and mucosal melanoma**
- **15% mutation**
- **50%-65% V600E mutation**
- **Amplified in 10%-15%**
- **Amplified in 10%-15%**
- **Amplified in 30%**
- **Amplified in 30%**
- **Amplified in 20%**
- **Amplified in 15%-10%**
- **Amplified in 10%**
- **25%-50% loss**
- **25%-50% loss**
- **25%-50% loss**
- **Frequent loss**

Combination: BRAF (GSK436) plus MEK inhibitor (GSK212)
Dabrafenib plus Trametinib

5 CR: 3 confirmed, 2 waiting follow-up
4 pts not shown on plot: 2 PR, 1 SD, 1 PD

GSK436 75 mg BID/GSK212 1 mg QD
GSK436 150 mg BID/GSK212 1 mg QD
GSK436 150 mg BID/GSK212 1.5 mg QD
GSK436 150 mg BID/GSK212 2 mg QD

ASCO 2011 Kefford et al
Dabrafenib vs Dabrafenib+Trametinib
Progression-Free Survival

Estimated survival function

Time since randomization (months)

Patients at risk

1.0
0.8
0.6
0.4
0.2
0.0

0
3
6
9
12
15
18

54
54
54

46
47
52

25
33
36

13
26
29

12 mo. PFS rate

54
46
33
13
2
11
2

9%
26%
41%

Med follow up time 14 mo

Mono D
150/1
150/2

Med (mos)
5.8
9.2
9.4

HR (95% CI), P-Value
0.56 (0.37, 0.87), 0.006
0.39 (0.25, 0.62), <0.0001
Drabrafenib vs Dab+Trametenib  Overall Survival

Estimated survival function

Patients at risk

Med follow up time 14 mo

43/54 (80%) Monotherapy D crossed to 150/2

Median OS rate

12 mo. OS rate

Mono D  
150/1  NR  0.98, NS  68%
150/2  NR  0.67, NS  79%

HR, P-Value

70%

Med follow up time 14 mo
GDC-0973:
- Orally available, potent and highly selective small-molecule inhibitor of both MEK 1 and MEK 2
- GDC-0973 monotherapy Phase I study:
  - 14 day on/14 day off schedule MTD = 100mg
  - 21 day on/7 day off schedule MTD = 60mg
  - Common AEs: diarrhea, rash, edema, fatigue, nausea
  - Encouraging single-agent activity in BRAF$^{V600}$ melanoma
    - 7 responders out of 12 melanoma patients
    - 6 responders were BRAF$^{V600E}$ mutation-positive (1 pt unknown mutation status)
    - Median time on GDC-0973 treatment: 9.3 months (range 1.4 - 23 months).

BRIM7 Objectives:
- To evaluate the safety and tolerability of vemurafenib + GDC-0973
- To identify the dose-limiting toxicities (DLTs) that determine the maximum tolerated dose (MTD) of vemurafenib + GDC-0973
- To identify a Phase II/III dose and schedule for vemurafenib + GDC-0973
BRIM7 Results: Change in tumor size from baseline to best response in BRAFi-naïve patients

Best Tumor Response for Each Patient (BRAFi-naïve)

% Change from Baseline in SLD of Target Lesions

Individual Patients Treated with Vemurafenib and GDC-0973

SLD, sum of longest diameters

n=25 evaluable patients

Gonzalez, R. et al ESMO 2012
NRAS-mutant melanoma

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median OS (y)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WT</strong></td>
<td>94</td>
<td>1.3</td>
<td>------</td>
</tr>
<tr>
<td><strong>BRAF with inhibitor</strong></td>
<td>41</td>
<td>NR</td>
<td>.02</td>
</tr>
<tr>
<td><strong>BRAF without inhibitor</strong></td>
<td>112</td>
<td>0.9</td>
<td>.10</td>
</tr>
<tr>
<td><strong>NRAS</strong></td>
<td>66</td>
<td>0.7</td>
<td><strong>.003</strong></td>
</tr>
</tbody>
</table>

Inhibitors: PLX-4032; GSK-2118436; GSK-1120212; AZD-6244
MEK inhibitors in NRAS mutant melanoma

- RTKs
- SOS
- PI3K/AKT/mTOR pathway
- NRAS
- MEK
- B-RAF
- C-RAF
- ERK1/2
- p90RSK
- MSK1

MEKi:
- selumetinib
- trametinib
- pimasertib
- MEK162
- GDC0973

Proliferation, Survival
MEK162 NRAS mutant melanoma

Best ORR 28%

*Patients with missing best % change from baseline and unknown overall response are not included.
Drug Development Challenges

- **Tumor by evolution is “moving target”**
  - Heterogeneity and Innate resistance
  - Acquired resistance/Additional mutations
  - Tumor cell plasticity EMT-MET
  - Cancer Stem Cells
  - Epigenetics

- **MONO-DIMENSIONAL THINKING ABOUT PATHWAYS**
Would not have been predicted by Geneprofiling
Needed shRNA screening
A map of human cancer signaling

Qinghua Cui¹, Yun Ma², Maria Jaramillo³, Hamza Bari¹, Arit Awan¹, Song Yang⁴, Simo Zhang², Lixue Liu², Meng Lu², Maureen O'Connor-McCourt³, Enrico O Purisima¹,⁵ and Edwin Wang¹,⁵.

Figure 3. Human oncogene-signaling map. The human cancer-signaling map was extracted from the human signaling network, which was mapped with cancer signaling network.
THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION
IMMUNOTHERAPY ESTABLISHED
“targeted therapy”

ANTI-CTLA4
Anti CTLA-4 Monoclonal Antibodies
Perpetuate T Cell Activation
Reawaken silenced Immune Response
## Ipilimumab in Melanoma in 2nd line

### Survival Rate

<table>
<thead>
<tr>
<th></th>
<th>Ipi + gp100 N=403</th>
<th>Ipi + pbo N=137</th>
<th>gp100 + pbo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>2 year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
</tr>
</tbody>
</table>

### Comparison

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms A vs. C</td>
<td>0.68</td>
<td>0.0004</td>
</tr>
<tr>
<td>Arms B vs. C</td>
<td>0.66</td>
<td>0.0026</td>
</tr>
</tbody>
</table>
Ipilimumab + DTIC in Melanoma in 1\textsuperscript{st} line. IMPACT MEDIAN SURVIVAL 2.1 MONTHS

Activity and Biomarkers

**Activity**

- **ORR 10-15%**
- Takes often > 3 months, may have initial PD
- Tail on curve: about 20% > 2-3 years control
- Combo with chemo: disappointing / no clear gains

**Biomarkers**

- No Good Predictive Biomarkers
  - Lymphocyte count
  - Eosinophil count
  - irAEs
TOXICITY Ipilimumab

Not so easy to handle

“Autoimmune Events” irAE

- Colitis
- Dermatitis
- Hepatitis
- Hypophysitis
- Thyroiditis
DRUG OF THE YEAR

ANTI-PD1/PD1-L
Reminder

Anti-CTLA4 is quite different from Anti-PD-1
Anti-CTLA-4 Monoclonal Antibodies (CENTRAL AT LYMPHNODES)
Perpetuate T Cell Activation / Reawaken silenced Immune Response

Antigen

APC

IL-2

TCR

CD28

MHC

B7

CTLA-4

mAb

T-cell

Antigen

CD28

MHC

B7

Anti-CTLA-4 mAb
PD-1 — PDL-1
ACTION MAINLY AT TUMOR SITE

D Pardoll Nat Rev Cancer 2012
Blocking CTLA-4 and PD-1

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)

Activation (cytokines, lysis, proliferation, migration to tumor)
Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D.,
Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D.,
Neil H. Segal, M.D., Ph.D., Charlotte E. Arriyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N.,
Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N.,
Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D.,
Israel Lowy, M.D., Ph.D., Hector David Inznunza, M.D., William Feely, M.S.,
Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D.,
Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

ABSTRACT

BACKGROUND
In patients with melanoma, ipilimumab (an antibody against cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) prolongs overall survival, and nivolumab (an antibody against the programmed death 1 [PD-1] receptor) produced durable tumor regression in a phase 1 trial. On the basis of their distinct immunologic mechanisms of action and supportive preclinical data, we conducted a phase 1 trial of nivolumab combined with ipilimumab in patients with advanced melanoma.

METHODS
We administered intravenous doses of nivolumab and ipilimumab in patients every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses (concurrent with ipilimumab). Safety and efficacy were evaluated in patients who received nivolumab alone, ipilimumab alone, or both. From the Ludwig Center, Memorial Sloan-Kettering Cancer Center, New York (J.D.W., M.K.C., M.A.P., N.A.R., A.M.L.,
N.H.S., C.E.A., R.A.G., S.A.K., B.U.A.); Yale University School of Medicine and Smilow Cancer Center, Yale New Haven Hospital, New Haven, CT (H.K., K.R.,
M.M.B., A.C., M.S.); Dako North America, Carpinteria (X.Z.); and Bristol-Myers Squibb, Redwood City (A.J.K.) — both in California; and Bristol-Myers Squibb, Princeton, NJ (I.L., H.D.I., W.F., C.E.H., Q.H.,
J.M.W., A.G.). Address reprint requests to
IPILIMUMAB + NIVOLIMUMAB
Best Responses in Sequenced Cohorts

Patients who had radiographic progression with prior ipilimumab treatment.
Patients who had stable disease with prior ipilimumab treatment.

Presented by: Jedd D. Wolchok, MD, PhD
After ~13 months of follow-up, for all concurrent cohorts, 90% of all responding patients continue to respond as of Feb 2013.
## Preliminary Best Overall Response of MK-3475 (LAMBROLIZUMAB)

### 135 Advanced MEL Patients

<table>
<thead>
<tr>
<th></th>
<th>Complete Response (N, 95% CI)</th>
<th>Objective Response (N, 95% CI)</th>
<th>Disease Control Rate (N, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All MEL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=85</td>
<td>9% (8; 4% -18%)</td>
<td>51% (43; 39 % -61%)</td>
<td>59% (50; 48% -69%)</td>
</tr>
<tr>
<td><strong>IPI Naïve</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=58</td>
<td>14% (8; 6% -25%)</td>
<td>55% (32; 41% -68%)</td>
<td>64% (37; 50% -76%)</td>
</tr>
<tr>
<td><strong>IPI Treated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=27</td>
<td>0% (0)</td>
<td>41% (11; 22% -61%)</td>
<td>48% (13; 29% -68%)</td>
</tr>
</tbody>
</table>

All patients were dosed at 10 mg/kg
Includes all patients who received first dose as of April 25, 2012.
Investigator reported response information as of October 19, 2012.
Objective response= confirmed and unconfirmed complete and partial response
Disease control rate= objective response + stable disease

LAMBROLIZUMAB: Characteristics of Responses (irRC):
Time to Respond & Duration for 43 Patients with Objective Response

- Median duration of treatment, 7.6 months + (3.3-11+)
- One patient discontinued due to PD and four patients discontinued due to AEs
Nivolimumab / Lambrolizumab in Melanoma

- **Long Term Data Nivolimumab:**
  - Response rates around 30%
  - MEDIAN DURATION of RESPONSE: > 2 YEARS!

- **Lambrolizumab alone**
  - Response rates up to 50-60%

- **Ipilimumab + Nivolimumab**
  - Response Rates up to > 80%
  - MAJORITY > 80% REGRESSION
Combining immunotherapy and targeted therapy for melanoma?
Hepatotoxicity with Combination of Vemurafenib and Ipilimumab

Antoni Ribas, M.D., Ph.D.
University of California Los Angeles
Los Angeles, CA

F. Stephen Hodi, M.D.
Dana–Farber Cancer Institute
Boston, MA

Margaret Callahan, M.D., Ph.D.
Memorial Sloan-Kettering Cancer Center
New York, NY

Cyril Konto, M.D.
Bristol-Myers Squibb
Wallingford, CT

Jedd Wolchok, M.D., Ph.D.
Memorial Sloan-Kettering Cancer Center
New York, NY

---

Table 1. Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab.

<table>
<thead>
<tr>
<th>Study Cohort and Patient No.</th>
<th>No. of Doses of Ipilimumab before ALT-AST Elevation</th>
<th>Time to Onset of ALT-AST Elevation after First Dose of Ipilimumab</th>
<th>Treatment</th>
<th>Time to Resolution of ALT-AST Elevation</th>
<th>Toxicity Relapse with Repeated Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>21 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>4 days</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>36 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (2 doses)</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>6+</td>
<td>1</td>
<td>21 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab continued (1 dose)</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>19 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (1 dose)</td>
<td>12 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Second cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>15 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>10 days</td>
<td>NA</td>
</tr>
<tr>
<td>16+</td>
<td>1</td>
<td>13 days</td>
<td>Vemurafenib and ipilimumab permanently discontinued</td>
<td>20 days</td>
<td>NA</td>
</tr>
</tbody>
</table>
Ipilimumab vs Ipilimumab + GM-CSF
- Less Toxicity ?
- Survival Benefit for Combo
- Unexplained ....

T-VEC
- Response rates 16%
- Survival benefit ??
Patients were to remain on treatment beyond progression unless clinically significant (i.e., associated with reduced performance status) after 24 weeks.

* Dosing of intralesional T-VEC was ≤ 4 mL x 10^6 pfu/mL once, then after 3 weeks, ≤ 4 mL x 10^8 pfu/mL Q2W. Dosing of GM-CSF was 125 μg/m² subcutaneous daily x 14 days of every 28 day cycle.
T-VEC: An HSV-1 Derived Oncolytic Immunotherapy Designed to Produce Both Local and Systemic Effects

Local Effect: Tumor Cell Lysis

Systemic Effect: Tumor-Specific Immune Response

Selective viral replication in tumor tissue

Tumor cells rupture for an oncolytic effect

Systemic tumor-specific immune response

Death of distant cancer cells

T-VEC key genetic modifications:

JS1/ICP34.5-/ICP47-/hGM-CSF

Method of Administration

- T-VEC administered into cutaneous, SC, or nodal lesions (+/- ultrasound guidance)
- No injections of visceral lesions permitted
- Limits on amount to be injected per lesion by size (see table)
- No specific limits on number of lesions injected per visit
- Precedence to be given to new lesions, then larger lesions

<table>
<thead>
<tr>
<th>Lesion size (diameter)</th>
<th>T-VEC injection volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5.0 cm</td>
<td>≤ 4.0 mL</td>
</tr>
<tr>
<td>&gt; 2.5 cm to 5.0 cm</td>
<td>≤ 2.0 mL</td>
</tr>
<tr>
<td>&gt; 1.5 cm to 2.5 cm</td>
<td>≤ 1.0 mL</td>
</tr>
<tr>
<td>&gt; 0.5 cm to 1.5 cm</td>
<td>≤ 0.5 mL</td>
</tr>
<tr>
<td>≤ 0.5 cm</td>
<td>≤ 0.1 mL</td>
</tr>
</tbody>
</table>

This total dose administered in any one treatment session should not exceed 4.0 mL.
Secondary Endpoint: Time to Treatment Failure

- Time to treatment failure was defined as time from the first dose of study treatment until death or development of clinically significant progressive disease (PD) per investigator for which no objective response was subsequently achieved.
- Patients who withdrew prior to development of clinically significant PD were censored at the time of the last assessment.

Study Month

```
<table>
<thead>
<tr>
<th>Risk set, n</th>
<th>T-VEC (N = 295)</th>
<th>GM-CSF (N = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-VEC</td>
<td>175</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
```

```
Median (95% CI)
```

- T-VEC (N = 295): 8.2 (6.5, 9.9) months
- GM-CSF (N = 141): 2.9 (2.8, 4.0) months

Log Rank: $P < 0.0001^*$
Hazard Ratio: 0.42 (0.32, 0.54)

*P-value is descriptive only
Interim Overall Survival

- Interim OS data represent >85% (250 of 290) of the required events for the primary analysis of OS
- 290 events required to demonstrate a OS HR of 0.67 with 90% power

Median (95% CI)
- T-VEC (N = 295): 23.3 (19.4, 29.7) months
- GM-CSF (N = 141): 19.0 (16.0, 24.0) months

Log Rank: $P = 0.07^*$
- HR: 0.79 (0.61, 1.02)

Survival Difference

<table>
<thead>
<tr>
<th>Survival</th>
<th>T-VEC</th>
<th>GM-CSF</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month</td>
<td>73.7%</td>
<td>69.4%</td>
<td>4.3 (-4.9, 13.5)</td>
</tr>
<tr>
<td>24-month</td>
<td>49.6%</td>
<td>41.3%</td>
<td>8.3 (-1.9, 18.5)</td>
</tr>
<tr>
<td>36-month</td>
<td>40.6%</td>
<td>27.8%</td>
<td>12.8 (1.0, 24.6)</td>
</tr>
</tbody>
</table>
STAGE IV Melanoma

❖ IMMUNOTHERAPY to SWEEPS THE FIELD:
❖ `first line for all?
  → Except rapid BRAF+ rapid progressors (25%) : BUY TIME
  → Anti-PD1
  → Anti-PD-1 + anti-CTLA4
  → Anti-PD1 + Targeted agents / or sequential?

❖ TARGETED THERAPIES
  → BRAFinh + MEKinh (+ ERKinh ?)
  → Combo + immuno? / sequential
  → Vemurafenib + Ipilimumab Failure (NEJM 2013)

❖ NEW TARGETS
  → PI3Kinhibitors?
  → MDM4? / p53? / MIA? etc

❖ ENDLESS COMBINATION POSSIBILITIES
Clinic
- Caroline Robert
- Christina Mateus
- Emilie Routier
- Laurent Maksimovic
- Kristina Opletalova
- Gwendoline Sebille
- Robert Baran
- Gilles Degois
- Bertrand Bachollet
- Beatrix Reynaud
- Florence Weil
- Richard Encaoua
- Gorana Tomasic
- Andrea Cavalcanti
- Frederic Kolb
- Benjamin Serfati

Clinical Research
- Imane Hamoum
- Severine Roy
- Saliou Camara
- Karine Waille
- Aliosha Celibic
- Gloria Le Brat
- Bruno Thuillier
- Paquita Lannes
- Laury Cherot
- Flore Dupuy
- Elodie Jezequel
- Emilie Lanoy
- Janine Wechsler
- Frederika Perrier

Translational Research
- Stephan Vagner
- Lise Boussemart
- Nyam Kamsu Kom
- Helene Mahieu-Malka
- Isabelle Girault
- Aicha Goubar
- Ludovic Lacroix
- Sandrine Agoussi
- Laurence Zitvogel
- Salem Chouaib
- Brigitte Bressac
- Christian Auclair
- Alexander Eggermont
COME VISIT GUSTAVE ROUSSY CANCER CENTER

THANK YOU