Avances en el tratamiento del melanoma

Antoni Ribas, M.D.
Professor of Medicine
Professor of Surgery
Professor of Molecular and Medical Pharmacology
at the University of California Los Angeles (UCLA)
Director, Tumor Immunology Program
at the Jonsson Comprehensive Cancer Center (JCCC)
Chair, Melanoma Committee at SWOG
Two Paradigms for Advancing the Therapy of Metastatic Melanoma

Targeted Immunotherapy

Target host

Targeted Oncogene Therapy

Target tumor
High dose IL-2 and Ipilimumab: The major benefit is in durable tumor regressions

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O’Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John R. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akedley, M.D., Alfons J.M. van der Eetraig, M.D., Ph.D., Jose Luzyk, M.D., Paul Luriggi, M.D., Julia M. Vauble, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensteiner, M.D., Ph.D., Celeste Lebbe, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph D. Clark, M.D., Jed D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Lien, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hocks, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

Impact on the tail of the curve!
“Miracle survivors”: A reproducible event with CTLA4 blocking monoclonal antibodies

CTLA4 response since 2003

CTLA4 response since 2004
Ipilimumab (Yervoy)

- Positive impact in overall survival in two randomized clinical trials using different schedules and combinations:
  - FDA approval with a broad label

- The major benefit is evident in a small population of patients (10-15%, most probably cured)

- Responses usually take time (1-4 months) to declare, and may go through a period of uncertainty about response or progression

- Clinically-significant inflammatory and immune toxicities in approximately 15-20% of patients
Two Paradigms for Advancing the Therapy of Metastatic Melanoma

Targeted Immunotherapy

Targeted Oncogene Therapy

Target host

Target tumor
Driver Oncogenic Mutations Define Clinically Relevant Melanoma Molecular Subsets

<table>
<thead>
<tr>
<th>Location</th>
<th>BRAF</th>
<th>NRAS</th>
<th>KIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin without chronic sun damage</td>
<td>50%</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin with chronic sun damage</td>
<td>10%</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Mucosal surfaces</td>
<td>5%</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>Acral surfaces</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Uveal melanoma</td>
<td>25%</td>
<td>55%</td>
<td></td>
</tr>
</tbody>
</table>

Curtin et al. NEJM 2005; Curtin et al. JCO 2006; Van Raamsdonk et al., NEJM 2010
Inhibition of MAPK signaling in biopsies of BRAF\textsuperscript{V600} melanoma from patients treated with vemurafenib (PLX4032)
PET Scans at Baseline and Day 15 after PLX4032

Before d+15

#69 MDA

#48 UCLA

Before d+15

#56 Vanderbilt

#59 Peter MacCallum
Waterfall plot of melanoma tumor responses with vemurafenib: Phase 1 study (32 patients)

The NEW ENGLAND JOURNAL of MEDICINE

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

Keith T. Flaherty, M.D., Igor Pazanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D.,
Gram A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D.,
Joseph F. Grippi, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.
Waterfall plot of melanoma tumor responses with vemurafenib: BRIM2 study (132 patients)

Response plots in melanoma before BRAF inhibitors

"Geyser plot"
Response plots in melanoma after BRAF inhibitors

Waterfall plot
A promising new melanoma drug rapidly and dramatically shrinks malignant tumors with very mild side effects, according to a new study.

In a highly encouraging but small trial, 27 advanced skin cancer patients were given the experimental drug PLX4032, and so far, 19 have shown a 30 percent or greater reduction in tumor size.

“We are seeing some pretty dramatic and rapid responses, and they are occurring in sites where we rarely see responses to chemotherapy, such as in the bone,” says co-investigator Dr. Paul Chapman of Memorial Sloan-Kettering Cancer Center in New York City.

“We’ve had patients come off oxygen, and we’ve got several patients who have been able to come off narcotic pain medication soon after starting treatment. I’ve never seen anything like it.”

A large international trial of PLX4032 is slated to start early next year.
Overall survival (12/30/10 cutoff)

Hazard ratio 0.37 (95% CI; 0.26 - 0.55)
Log-rank P<0.0001

= 63% decrease in the risk of being dead compared to chemotherapy

Chapman et al. ASCO 2011
## BRIM2: Toxicities with vemurafenib

Includes AEs reported in ≥20 patients

<table>
<thead>
<tr>
<th></th>
<th>All grades n (%)</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>130 (99)</td>
<td>79 (60)</td>
<td>5 (4)†</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>78 (59)</td>
<td>8 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Rash</td>
<td>69 (52)</td>
<td>9 (7)</td>
<td>–</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>69 (52)</td>
<td>4 (3)</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56 (42)</td>
<td>2 (2)</td>
<td>–</td>
</tr>
<tr>
<td>Alopecia</td>
<td>48 (36)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pruritus</td>
<td>38 (29)</td>
<td>3 (2)</td>
<td>–</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>38 (29)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>cuSCC / KA‡</td>
<td>34 (26)</td>
<td><strong>34 (26)</strong></td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (23)</td>
<td>2 (2)</td>
<td>–</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>23 (17)</td>
<td>8 (6) §</td>
<td>4 (3)¶</td>
</tr>
</tbody>
</table>

†One patient with 2 grade 4 AEs
‡Cases of cuSCC/KA were generally managed with simple excision and did not generally require dose modification
§Managed with dose reduction; one removed from study
¶Led to discontinuation of therapy
cuSCC/KAs with vemurafenib

• cuSCC/KAs:
  – Incidence: 26%
  – Median time 8 weeks (2–36)
  – Median number of cuSCC/KAs per patient 1 (range 1 to 7)
  – Each dot represents weeks to development of first cuSCC/KA lesion
cuSCC/KAs with vemurafenib

Torso
No RAS mutation

Left chest
KRAS\(^{G12D}\)

Chin
HRAS\(^{Q61L}\)

Left scalp
HRAS\(^{Q61L}\)

Courtesy of Grant McArthur (Peter Mac, Melbourne) and Roger Lo (UCLA)
Differential effects of BRAF inhibition in $BRAF^{V600}$ mutant melanoma and BRAF wild type cells

$BRAF^{V600}$ mutant melanoma

$BRAF$ wild type cells

Paradoxical MAPK activation in HRAS mutant cuSCC/KAs

**BRAF^V600** mutant melanoma  

**BRAF** wild type cells

Acquired Resistance to vemurafenib: Time to response and progression

BRIM2 study

Median duration of response = 6.7 months (95% CI: 5.6, 9.8; range 1.3–12.7)
Response and relapse with vemurafenib

10/02/08 (Pre)  11/26/08 (2+ mo)  02/20/09 (4+ mo)

LETTER

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

Ramin Nazarian1,2,*; Hubing Shi1,2; Qi Wang3,5; Xiangli Kong1,2; Richard C. Koya5,6; Hane Lee1,2; Zugen Chen2,4; Mi-Kyung Lee1,2; Narsis Attar1,2; Hooman Sazegar3,4; Thinek Chodon1,2; Stanley F. Nelson3,4,6; Grant McArthur7; Jeffrey A. Sosman1; Antoni Ribas1,5,*; & Roger S. Lo2,*
Mechanisms of Resistance to BRAF Inhibitors

NRASQ61

BRAF

CRAF

COT

MEKi

BRAFinh

MEK-dependent progression

PI3Ki or AKTi

PI3K

AKT

PDGFRb or IGF1R

Survival

MEK-independent progression

NRASQ61

Nazarian et al. Nature 2010

Johannessen et al. Nature 2010

Nazarian et al. Nature 2010

Villanueva et al. Cancer Cell 2010

Poulikakos et al. Nature in press

Poulikakos et al. JCO 2011

Johannessen et al. Nature 2010

Villanueva et al. Nature in press

Nature 2010

BRAFinh

CRAF

COT

MEKi

Survival

MEK-independent progression
Two Paradigms for Advancing the Therapy of Metastatic Melanoma

Targeted Immunotherapy

Target host

Targeted Oncogene Therapy

Target tumor
Combining immunotherapy and targeted therapy for melanoma?

**Immunotherapy**
![Graph showing improved survival with Ipilimumab in patients with metastatic melanoma.](image)

**Targeted therapy**
![Graph showing improved survival with Vemurafenib in melanoma with BRAF V600E mutation.](image)

**Combination**
![Graph showing percent alive for combination therapy.](image)
PLX4032 to Improve Immunotherapy

Selective BRAF\(^{V600E}\) Inhibition Enhances T-Cell Recognition of Melanoma without Affecting Lymphocyte Function

Andrea Boni, Alexandra P. Cogdill, Ping Dang, Durga Udayakumar, Ching-Ni Jenny Njauw, Callum M. Sloss, Cristina R. Ferrone, Keith T. Raherty, Donald P. Lawrence, David E. Fisher, Hensin Tsao, and Jennifer A. Wargo

DOI:10.1158/1078-0432.CCR-10-1911

The Oncogenic BRAF Kinase Inhibitor PLX4032/RG7204 Does Not Affect the Viability or Function of Human Lymphocytes across a Wide Range of Concentrations

Begoña Comín-Andúix\(^1,2\), Thinle Chodon\(^3\), Hooman Saezgar\(^3\), Douglas Matsunaga\(^3\), Stephen Mock\(^3\), Jason Jaffe\(^3\), Helena Esclun-Ordinas\(^3\), Bartosz Chmielowski\(^3\), Richard C Koya\(^1\), and Antoni Ribas\(^1,2,3\)
Abstract 958: Treatment with a selective inhibitor of BRAFV600E increases melanocyte antigen expression and CD8 T cell infiltrate in tumors of patients with metastatic melanoma.

Jennifer A. Wargo, Alex Cogdill, Ping Dang, Ridhi Gupta, Adriano Piris, Andrea Boni, Haven R. Garber, Harald Ott, Lindsay P. Newton, Keith T. Flaherty, Donald P. Lawrence, Hensin Tsao, David E. Fisher. MGH, Boston, MA

Abstract 656: Antitumor activity of combined therapy with the class I BRAF inhibitor PLX4032 and immunotherapy

Richard C. Koya, Stephen Mok, Nicholas Otte, Begonya Comin-Anduix, Thinle Chodon, Antoni Ribas. UCLA, Los Angeles, CA
Conclusions

• “2011: The year of melanoma”
  – George Sledge, MD, President of ASCO

• Scientific advances revert into improved patient care

• The mechanism of resistance to BRAF inhibitors predict for sensitivity to the addition of secondary treatments:
  – MEK inhibitors
  – PI3K/AKT/mTOR inhibitors

• Combining immunotherapy and BRAF targeted therapy in the clinic is warranted
Acknowledgements

Ribas lab:

Roger S. Lo, M.D., Ph.D.
Ramin Nazarian, Ph.D.
Hubing Shi, Ph.D.
James S. Economou, M.D., Ph.D.
Bartosz Chmielowski, M.D., Ph.D.
John A. Glaspy, M.D., M.P.H.

Earl Aramis
Nicholas Otte
Lidia Robert, M.D.
Mohammad Atefi, Ph.D.
Deborah Wong, M.D.

Vanderbilt: Jeff Sosman, M.D.
Peter Mac: Grant McArthur, M.D., Ph.D.
MGH: Keith Flaherty, M.D.
MSKCC: Paul Chapman, M.D., Neil Rosen, M.D.,
David Solit, M.D.
ICR, London: Richard Marais, Ph.D.
Plexxikon: Gideon Bollag, Ph.D.