Update on Targeted Therapy in Melanoma

Seville June 2013

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PhD
London UK
Overview

• What are the targets in melanoma?
• BRAF / KIT / NRAS / GNAQ / MEK
• DNA / microtubules
• CTLA4 / PD1 / PDL1
• Challenges for targeted therapy
Overview

• What are the targets in melanoma?
• BRAF / KIT / NRAS / GNAQ / MEK
• DNA / microtubules
• CTLA4 / PD1 / PDL1

• Challenges for targeted therapy
The story starts here...
The story starts here...

Mutations of the BRAF gene in human cancer

Helen Davies¹,², Graham R. Bignell¹,², Charles Cox¹,², Philip Stephens¹,², Sarah Edkins¹, Sheila Clegg¹, Jon Teague¹, Hayley Woffenden¹, Mathew J. Garnett³, William Bottomley¹, Neil Davis¹, Ed Dicks¹, Rebecca Ewing¹, Yvonne Floyd¹, Kristian Gray¹, Sarah Hall¹, Rachel Hawes¹, Jaime Hughes¹, Vivian Kosmidou¹, Andrew Menzies¹, Catherine Mould¹, Adrian Parker¹, Claire Stevens¹, Stephen Watt¹, Steven Hooper³, Rebecca Wilson³, Hiran Jayatilake⁴, Barry A. Gusterson⁵, Colin Cooper⁶, Janet Shipley⁶, Darren Hargrave⁷, Katherine Pritchard-Jones⁷, Norman Maitland⁸, Georgia Chenevix-Trench⁹, Gregory J. Riggins¹⁰, Darell D. Bigner¹⁰, Giuseppe Palmieri¹¹, Antonio Cossu¹², Adrienne Flanagan¹³, Andrew Nicholson¹⁴, Judy W. C. Ho¹⁵, Suet Y. Leung¹⁶, Siu T. Yuen¹⁶, Barbara L. Weber¹⁷, Hilliard F. Seigler¹⁸, Timothy L. Darrow¹⁸, Hugh Paterson³, Richard Marais³, Christopher J. Marshall³, Richard Wooster¹,⁶, Michael R. Stratton¹,⁴ & P. Andrew Futreal¹
Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D.,
John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D.,
Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D.,
Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D.,
Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D.,
Antoni Ribas, M.D., Steven J. O’Day, M.D., Jeffrey A. Sosman, M.D.,
John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D.,
Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A.,
Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D.,
and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*
Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma

Keith T. Flaherty, M.D., Caroline Robert, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Paul Nathan, M.D., Ph.D., Claus Garbe, M.D., Mohammed Milhem, M.B., Lev V. Demidov, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Peter Mohr, M.D., Reinhard Dummer, M.D., Uwe Trefzer, M.D., James M.G. Larkin, M.D., Jochen Utikal, M.D., Brigitte Dreno, M.D., Marta Nyakas, M.D., Mark R. Middleton, Ph.D., Jürgen C. Becker, M.D., Ph.D., Michelle Casey, Ph.D., Laurie J. Sherman, R.N., Frank S. Wu, M.D., Ph.D., Daniele Ouellet, Ph.D., Anne-Marie Martin, Ph.D., Kiran Patel, M.D., and Dirk Schadendorf, M.D., for the METRIC Study Group*
Abnormal Cellular Proliferation

RTK e.g. KIT

NRAS

BRAF

KIT ~ 2%
BRAF ~ 50%
NRAS ~ 20%
GNAQ ~ 2%

Curtin NEJM 2005; Curtin JCO 2006
RAF
MEK
ERK

Cellular
Proliferation

NRAS
BRAF
V600E

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Abnormal Cellular
Proliferation

Curtin NEJM 2005; Curtin JCO 2006
BRAF
BRIM 3: Vemurafenib vs DTIC

48% confirmed response rate (2 complete responses)

5% confirmed response rate (0 complete responses)
BRIM 3: Vemurafenib vs DTIC

A Progression-free Survival

Hazard ratio, 0.26; 95% CI, 0.20 to 0.33; P<0.001

Progression-free Survival (%)

No. at Risk
Dacarbazine 274 213 85 48 28 16 10 6 3 0 0 0 0 0
Vemurafenib 275 268 211 122 105 50 35 16 4 3 0 0 0 0

Months
17 year old with advanced melanoma
Day 9 BRAF inhibitor therapy
95 year old with advanced melanoma
3 months of vemurafenib 480mg bd
Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffery R. Infante, M.D., Adil Daud, M.D., Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D., Omid Hamid, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D., Nageatte Ibrahim, M.D., Ragini Kudchadkar, M.D., Howard A. Burris III, M.D., Gerald Falchook, M.D., Alain Algazi, M.D., Karl Lewis, M.D., Georgina V. Long, M.D., Ph.D., Igor Puzanov, M.D., M.S.C.I., Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shonda Little, M.P.H., Peng Sun, Ph.D., Alicia Allred, Ph.D., Daniele Ouellet, Ph.D., Kevin B. Kim, M.D., Kiran Patel, M.D., M.B.A., and Jeffrey Weber, M.D., Ph.D.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dabrafenib</th>
<th>Dabrafenib+trametinib 150/1</th>
<th>Dabrafenib+trametinib 150/2</th>
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<tbody>
<tr>
<td>Hyperkeratosis</td>
<td>30%</td>
<td>6%</td>
<td>9%</td>
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<tr>
<td>cuSCC</td>
<td>19%</td>
<td>2%</td>
<td>7%</td>
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<tr>
<td>Papillomas</td>
<td>15%</td>
<td>7%</td>
<td>4%</td>
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<tr>
<td>Pyrexia</td>
<td>26%</td>
<td>69%</td>
<td>71%</td>
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</table>

Lower toxicity related to paradoxical MAPK activation.
BRAF: The Future

• I think BRAFi + MEKi will become standard of care (Roche/Genentech, GSK, ?Novartis)
• Dabrafenib and trametinib recently FDA approved as single agents
• Adjuvant trials are underway (vemurafenib and dabrafenib+trametinib, both vs placebo)
• I think acquired resistance will remain the biggest clinical problem
RTK e.g. KIT

NRAS

BRAF<sup>V600E</sup>

MEK

ERK

Abnormal Cellular Proliferation

KIT ~ 2%
BRAF ~ 50%
NRAS ~ 20%
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MEK
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Cellular Proliferation

NRAS
BRAF
V600E

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NRAS ~ 20%
GNAQ ~ 2%

Abnormal Cellular Proliferation
KIT mutations

- KIT mutations
- Glutamic acid (E) glutamic acid
- Lysine (K) lysine
- Leucine (L) leucine
- Proline (P) proline

- Exon 17 < 10%
- K642E ~ 16%
- L576P ~ 33%
- Other Exon 11 ~ 33%
## Figure 1. Treatment Response Over Time by Melanoma Subtype and Genetic Alteration of KIT

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Mutation</th>
<th>Amplification (Ratio)</th>
<th>Amplified Pattern</th>
<th>Mutant: Wild-Type Ratio</th>
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<tbody>
<tr>
<td>Acréal</td>
<td>Ex 17 D820Y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (5-10)</td>
<td>Uniform</td>
<td>1:1</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Ex 9 N463S</td>
<td>No</td>
<td>NA</td>
<td>1:1</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Ex 11 L576P&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (&gt;10)</td>
<td>Mixed</td>
<td>1:1</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Ex 11 L576P&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (5-10)</td>
<td>Mixed</td>
<td>1:1</td>
</tr>
<tr>
<td>Mucosal</td>
<td>No</td>
<td>Yes (2.5-5)</td>
<td>Uniform</td>
<td>NA</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Ex 13 V654A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (2.5-5)</td>
<td>Mixed</td>
<td>1:1</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Ex 18 V8521</td>
<td>No</td>
<td>NA</td>
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<tr>
<td>CSD</td>
<td>Ex 11 Y570H</td>
<td>No</td>
<td>NA</td>
<td>1:1</td>
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<tr>
<td>Acréal</td>
<td>Ex 13 K642E&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No</td>
<td>NA</td>
<td>1:3</td>
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<tr>
<td>Mucosal</td>
<td>Ex 11 L576P&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (5-10)</td>
<td>Uniform</td>
<td>4:1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acréal</td>
<td>No</td>
<td>Yes (&gt;10)</td>
<td>Uniform</td>
<td>NA</td>
</tr>
<tr>
<td>Acréal</td>
<td>Ex 18 P838L</td>
<td>No</td>
<td>NA</td>
<td>1:0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Ex 18 A829P&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No</td>
<td>NA</td>
<td>1:3</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Ex 11 L576P&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No</td>
<td>NA</td>
<td>1:1</td>
</tr>
<tr>
<td>CSD</td>
<td>Ex 11 V559C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (&gt;10)</td>
<td>Uniform</td>
<td>1:1</td>
</tr>
<tr>
<td>CSD</td>
<td>No</td>
<td>Yes (5-10)</td>
<td>Mixed</td>
<td>NA</td>
</tr>
<tr>
<td>Acréal</td>
<td>Ex 13 K642E&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (5-10)</td>
<td>Uniform</td>
<td>3:1&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Mucosal</td>
<td>Ex 13 K642E&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (&gt;2.5)</td>
<td>Uniform</td>
<td>1:0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acréal</td>
<td>Ex 13 1653T</td>
<td>No</td>
<td>NA</td>
<td>1:5</td>
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<tr>
<td>CSD</td>
<td>Ex 17 N822K&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes (&gt;10)</td>
<td>Mixed</td>
<td>1:3</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Ex 11 L576P&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No</td>
<td>NA</td>
<td>1:1</td>
</tr>
<tr>
<td>Acréal</td>
<td>Ex 13 K642E&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>NA</td>
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<tr>
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<td>4:1&lt;sup&gt;b&lt;/sup&gt;</td>
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</table>

- Progression of disease
- Stable disease
- Transient partial response
- Durable partial response
- Durable complete response

Carvajal JAMA 2011
KIT Mutations in Melanoma: Challenges

• Difficulty of deciding whether a change in DNA/protein sequence is a driver (cf passenger)
• Difficulty of deciding a priori whether a mutation will be sensitive to drug therapy
• Different sequencing technologies have different characteristics
• Rarity and slowness of publication process: a registry/database would help
RAF
MEK
ERK

Cellular Proliferation

NRAS
RTK e.g. KIT

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Abnormal Cellular Proliferation

KIT ~ 2%
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Curtin NEJM 2005; Curtin JCO 2006
RAF MEK ERK Cellular Proliferation

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Curtin NEJM 2005; Curtin JCO 2006
NRAS
MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study


Ascierto Lancet Oncology 2013
NRAS: The Future

• Clear (although modest) activity of MEKi from early data
• Merck and Novartis pursuing randomised trials vs cytotoxics
• Is this activity going to be sufficient to beat promising early activity of anti-PD1 or anti-PD1+anti-CTLA4?
• I’m uncertain
Abnormal Cellular Proliferation

RTK e.g. KIT

NRAS

BRAF\text{V600E}

MEK

ERK

KIT \sim 2\%

BRAF \sim 50\%

NRAS \sim 20\%

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RTK e.g. KIT

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V600E

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GNAQ ~ 2%

Curtin NEJM 2005; Curtin JCO 2006
GNAQ/GNA11
Selumetinib in Uveal Melanoma

• No clear standard of care for advanced uveal melanoma
• Hints of activity for ipi from case series though
• Definite activity for MEKi selumetinib in prospective randomised phase 2 vs TMZ
• First ever prospective signal
• Provides foundation for further work
• Other promising approaches e.g. protein kinase C inhibitors e.g. AEB071
Challenges for Targeted Therapy

1) Resistance to therapy
2) Chronic side effects (compare cytotoxics)
3) Optimal scheduling
4) Adjuvant setting
5) Cost and access to treatment
Challenges for Targeted Therapy

1) Resistance to therapy
2) Chronic side effects (compare cytotoxics)
3) Optimal scheduling
4) Adjuvant setting
5) Cost and access to treatment
Resistance

• Resistance to targeted therapy almost universal (similar to cytotoxics for solid tumours)
• In melanoma, resistance mechanisms appear varied but are they predictable?
• Targeted therapy paradigm: predict resistance mechanism from the outset or sample tissue at progression, analyse and treat rationally (as opposed to best guess)
• In melanoma at least, this may not be easy; For e.g. in RMH patients treated with vemurafenib, 16/42 (38%) of patients were too ill after progression on vemurafenib to receive 2nd line therapy

Fisher SMR 2012
Intratumour Heterogeneity and Resistance

65% of mutations are heterogeneous and not shared in every biopsy

Gerlinger NEJM 2012
Phylogenetic Analyses Reveal Branched Evolution of Tumours

- Branched tumour evolution underscores the importance of targeting ubiquitous alterations in the trunk of the phylogenetic tree.

Gerlinger NEJM 2012
Is Understanding Resistance Tractable?

• Except in post-mortem studies, we can never sample all sites of metastatic disease
• Will tumours always be one step ahead because of their ability to evolve under selective pressure of therapy?

We agree with the requirement for postmortem studies to characterize heterogeneity at multiple sites of metastatic disease and to reveal evolutionary bottlenecks that may govern both the clonal evolution from localized to metastatic disease and the acquisition of drug resistance by tumors. Such studies face numerous regulatory and ethical challenges and will require close collaboration with patient-advocacy groups.

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Marco Gerlinger, M.D.
Cancer Research UK London Research Institute
London, United Kingdom

Gerlinger NEJM 2012
Resistance: possible solutions

- Knowledge of possible resistance mechanism from the start (e.g. presence of rare subclones detected pretreatment)
- Sensitive non-invasive methods to detect and characterise resistance early
- Combining targeted drugs is touted as a solution but I think this will just delay the emergence of resistance and not solve the problem
- Immunotherapy? Novel schedules?

Su JCO 2012 Das Thakur Nature, AACR 2013
Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.
<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Vemurafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Given how?</strong></td>
<td>Brief course intravenous</td>
<td>Continuous daily oral</td>
</tr>
<tr>
<td><strong>Side effects?</strong></td>
<td>Temporary</td>
<td>Chronic</td>
</tr>
<tr>
<td><strong>Severity?</strong></td>
<td>Can rarely be severe</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td><strong>Prolonged disease control?</strong></td>
<td>Possible</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Tumour shrinkage</strong></td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Who benefits?</strong></td>
<td>~15% across the board</td>
<td>Almost all with BRAF mutation</td>
</tr>
</tbody>
</table>
Immunotherapy

Targeted therapy

Combination???
Change in the management of patients

GET IN EARLY WITH
immune checkpoint blockade
Change in the management of patients

GET IN EARLY WITH immune checkpoint blockade

• Treatment takes time to work
• Don’t wait for patient to be poor prognosis
• Don’t wait for symptomatic CNS disease
• Use targeted agents as ‘rescue palliative therapy’
Change in the management of patients

Screen for 2^0^s in high risk patients (Stage 3)

CT TAP/MRI
Month 3 then 6-mthly for 3 years

Strategy to administer Ipilimumab early at first diagnosis of systemic 2^0^s

Targeted Therapy
Conclusions

• BRAFi/MEKi high response rate, prolonged PFS and OS in BRAF mutant

• Emerging data for KIT inhibitors in KIT mutant and MEKi in NRAS and GNAQ/GNA11 mutant

• Targeted therapy not curative, ipilimumab curative but small

• Resistance to targeted therapy: difficult clinical problem

• Combination of targeted therapies with immunotherapy likely major research focus
Thank you