Rol de los Inhibidores de MEK Melanoma

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Santarpia L. Expert Opin Ther Targets 2012
<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Common toxicity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trametinib (GSK1120212)</td>
<td>III</td>
<td>Retinopathy, rash, diarrhea</td>
<td>Approved monotherapy</td>
</tr>
<tr>
<td>Cobimetinib (XL518/GDC0973)</td>
<td>III</td>
<td>Rash, nausea, elevated CK</td>
<td>Ongoing trial</td>
</tr>
<tr>
<td>MEK162 (Arry 438162)</td>
<td>III, I</td>
<td>Rash, dermatitis, CKP</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Selumetinib (AZD6244)</td>
<td>II, III(uveal)</td>
<td>Rash, nausea, xerostomia</td>
<td>MEK1 (not dual) Not ongoing trials in cutaneous</td>
</tr>
<tr>
<td>PD0325</td>
<td>I</td>
<td>Rash, blurry vision, diarrhea</td>
<td>Retinal vein oclussion stop development</td>
</tr>
<tr>
<td>AZD8330/ARRY4247</td>
<td>I</td>
<td>Rash, change mental status, nausea</td>
<td>No ongoing trials</td>
</tr>
<tr>
<td>TAK733</td>
<td>I</td>
<td>-</td>
<td>No ongoing</td>
</tr>
<tr>
<td>ROS126766</td>
<td>I</td>
<td>Rash, diarrhea, CPK</td>
<td>Braf/MEK1/2</td>
</tr>
<tr>
<td>BAY86-9766</td>
<td>I</td>
<td>Hepa</td>
<td>Low activity. No ongoing</td>
</tr>
<tr>
<td>Pimasertib AST03026 (EMD)</td>
<td>I</td>
<td>Rash, nausea, visual disturbance</td>
<td>non-melanoma</td>
</tr>
<tr>
<td>CI-1040</td>
<td>I</td>
<td>-</td>
<td>Low activity</td>
</tr>
<tr>
<td>RO4987</td>
<td>I</td>
<td>Rash, GI disorders</td>
<td>MEK1</td>
</tr>
</tbody>
</table>
MEK inhibitors are different

GDC-0973 reduced efficacy in KRAS mutant in vivo models compared to GDC-0623 and GDC-573, the reverse was found in BRAF(V600E) models

BRAF mutant cutaneous melanoma

Trametinib. Phase III METRIC STUDY

OR 22% vs 8%
PFS 5 m vs 1.5 m
OS 6m 81% vs 67%

30% qt previously
**BRAF^V600**

**mutant melanoma**

- Improve ORR
- Prevent resistance (more durable responses and improved PFS)
- Improve OS

**Wild type normal cell**

- Decrease toxicities from paradoxical MAPK activation
GSK436 150 mg BID/GSK212 1 mg QD
GSK436 150 mg BID/GSK212 2 mg QD
GSK436 75 mg BID/GSK212 1 mg QD

Maximum % reduction from baseline measurement

83% of responses ongoing (1-12 mo f/y)
1% incidence of cuSCC

ASCO 2011, abstract #8503: Infante, J. R

GSK BRAFi+MEKi phase 1
- PFS 9.4 vs 5.8 m
- RO 76% vs 54%
- Response in 3/18 pt previously resistant to vemurafenib

**BRIM 3** RO 48%
After progression to BRAFi: OR 15%
9010: Updated overall survival (OS) for BRF113220, a phase 1/2 trial of dabrafenib (D) alone versus combined dabrafenib + trametinib (D+T) in pts with BRAF V600 mutation-positive metastatic melanoma (MM).

Flaherty, Daud, Weber, Kim, Gonzalez, Hamid, Infante, Cebon, Schumacher, Noffsinger, Kudchakdar, Puzanov, Lawrence, Kline, Cunningham

First FDA approval of the combination of two oncogene targeted therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, mo (95% CI)</th>
<th>12-mo OS rate (%)</th>
<th>24-mo OS rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150/2 (N=54)</td>
<td>25.0 (17.5, NR)</td>
<td>80</td>
<td>51</td>
</tr>
</tbody>
</table>

Presented By Antoni Ribas at 2014 ASCO Annual Meeting
COMBI-d: Investigator-Assessed PFS
Data cut August 2013*

Dabrafenib + Trametinib
Med. PFS 9.3 mo
6 month PFS = 70%

Dabrafenib
Med. PFS 8.8 mo
6 month PFS = 57%

HR 0.75 (95% CI: 0.57, 0.99)
p=0.035

*Med f/u 9 months. 42% (dab) vs 53% (dab+tram) remained on study drug at data cut
Summary of responses and PFS of single agent BRAFi and BRAFi+MEKi combined therapy

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>III</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Agent</td>
<td>vemurafenib</td>
<td>dabrafenib</td>
<td>dabrafenib</td>
<td>dabrafenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dabrafenib +</td>
<td>dabrafenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>trametinib</td>
<td>trametinib</td>
</tr>
<tr>
<td>ORR</td>
<td>48%</td>
<td>50%</td>
<td>54%</td>
<td>76%</td>
</tr>
<tr>
<td>PFS</td>
<td>5.3 months</td>
<td>5.1 months</td>
<td>5.8 months</td>
<td>9.4 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>8.8 months</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>9.3 months</strong></td>
</tr>
</tbody>
</table>
BRIM 7 (fase Ib): Vemurafenib + GDC0973

BRAFi Naive OR 25/25
25 resistant patients: objectives response during MEKi, when stop MEKi: progression

Ribas T. ESMO 2013
MEK162: Phase II

RO BRAFV600 8/41 (20%), PFS 3.6m (longer with previous IP 5.5m vs 3.2m)

P Ascierto. Lancet 2013
Selumetinib (AZD6244)

Phase I

Adjei JCO 2008

Phase II Selu vs chemot: RO ns; in BRAFV600 RO 5/45 (11%)\(^1\)
Phase II Selu+DTIC vs DTIC: OR 40% vs 26%, PFS 6 vs 3 m; OS 14m vs 10.5 m (ns)
Phase I combination (dacarbazine, docetaxel, temsirolimus, or erlotinib)
18 pat (9 BRAF, 4 NRAS): OR in BRAF 56%, NRAS 0%

\(^1\)Kirwood, CCR18:555
\(^2\)Patel et al, Cancer 2013

**ASCO 2013 phase 1: selumet+/- AKTi (MK2206)**
(ongoing non-melanoma)
BRAF wild type melanomas: PAPSS1-BRAF is more sensitive to MEKi than BRAFi

NRAS mutant melanoma
Escape mechanisms: *NRAS* mutations

*Results from Sequenom Oncocarta Panels*

**ERK phosphorylation at progression**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age group</th>
<th>Stage</th>
<th>BOR</th>
<th>Archival/ baseline (n=90)</th>
<th>Progression (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Male</td>
<td>≤40</td>
<td>M1C</td>
<td>PR</td>
<td>WT</td>
<td>Q61K</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>55–64</td>
<td>M1B</td>
<td>PR</td>
<td>WT</td>
<td>Q61L</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>41–54</td>
<td>M1C</td>
<td>PR</td>
<td>–</td>
<td>Q61K</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>≤40</td>
<td>M1C</td>
<td>SD</td>
<td>Q61K</td>
<td>–</td>
</tr>
</tbody>
</table>

**Frequency of mutation in subgroup n/N (%)**

<table>
<thead>
<tr>
<th></th>
<th>1/90</th>
<th>3/13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(23)</td>
</tr>
</tbody>
</table>

Pre-therapy, *NRAS*, and *BRAF* mutations co-occurred at very low frequency

At disease progression (Van Allen 2014: all are in progression after 12 weeks)

- *NRAS*<sup>Q61</sup> mutations were noted in **3/13** patients
- persistence of *BRAF*<sup>V600</sup> mutations were detected in **13/14** samples

*Sosman et al. JCO 2012; 30 (suppl): 8503 ASCO 2012*
Clinical activity of MEKi in NRAS mutant melanoma

<table>
<thead>
<tr>
<th>Drug</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trametinib (GSK1120212)(^1)</td>
<td>0/9</td>
</tr>
<tr>
<td>Selumetinib (AZD6244) (^2)</td>
<td>0/9</td>
</tr>
<tr>
<td>MEK162(^3)</td>
<td>20%</td>
</tr>
</tbody>
</table>

1. Falchook. Lancet 2012
2. Kirwood. CCR 2012
3. Ascierto. Lancet Oncol 2013
MEK162 : Phase II

OR NRAS 6/30 (20%)

PFS 3.7m

Duration of resp 7.6 weeks

2 pat response in CNS

P Ascierto. Lancet 2013
Genentech GDC-0973

(A) A375.X1
(B) NCI-H2122

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Body weight change (%) vs Day

---

C
D

P-ERK/ERK (% of control) vs Time (h)
Other treatments: NRAS

Simvastatina → MEK INH → CDK4i

Flavopiridol → HSP90 → PI3Ki

HSP90

XIAP

IGF1R

Held et al. Cancer Discov 2013
Kwong Nat Med 2012
PD-0332991(CDK4/6i)+GSK 1120212(MEKi)

NRAS
mutant melanoma

NRAS

CRAF
BRAF

MEKi

MEK1/2

ERK

P

P

CCND1

CDK4/6

CR in 33% of mice

### Response, n (%) for CDK4/6i (LEE011)+MEKi (MEK162)

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>LEE011 + Binimetinib (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td></td>
</tr>
<tr>
<td>Confirmed PR</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Unconfirmed PR</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>11 (50)^a</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Unable to evaluate</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

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**Phase I (ASCO 2014) OR 82% (N 22)**

- **Complete response (CR):** 0%
- **Partial response (PR):** 7 (32%) (Confirmed PR: 3 (14%), Unconfirmed PR: 4 (18%))
- **Stable disease (SD):** 11 (50)^a
- **Progressive disease:** 3 (14%)
- **Unable to evaluate:** 1 (4%)

---

**Best Percentage Change from Baseline**

- **Treatment Group:**
  - LEE 200 mg + MEK 45 mg
  - LEE 300 mg + MEK 30 mg
  - LEE 250 mg + MEK 45 mg
  - LEE 300 mg + MEK 45 mg

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Posch C et al. PNAS 2013;110:4015-4020
Uveal melanoma
MEK-Dependent Genes in GNAQ Uveal Melanoma

Trametinib: Uveal Melanoma

**OR: 2/16 (24%) (1 mut GNAQ)**

» In GNAQ/11 SD 3/6

Infante/Falchook, 2012
Selumetinib (AZD6244)

Phase II, MEKi vs TMZ, n 98
SD 50%
PFS: 16 w vs 7 w
OS 11 m vs 9 m

Carvajal Memorial SK: ASCO 2013
MEK and/or PI3K inhibitors in GNAQ, GNA11 or wild-type uveal melanoma

Combined MEK and AKT inhibition results in antitumor effects in mouse xenografts.

PKC and MEK inhibition in uveal melanoma with GNAQ and GNA11 mutations

Chen. Oncogene 2013
MEKi resistance
Dynamic reprogramming kinome in response to MEKi

RTKs activated (PDGFRB, VEGFR2, HER3, AXL, DDR1)
Activity of MEKi + sorafenib or Fora (synthetic lethality)
Model of MEK inhibitor–induced feedback on ERBB receptor signaling

<table>
<thead>
<tr>
<th>MEK1Q56P</th>
<th>Acquired</th>
<th>COMBO</th>
<th>Year</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intrinsic</td>
<td>S</td>
<td>2013</td>
<td>Trunzer, Emeny 2009, Sosman 2012</td>
</tr>
<tr>
<td>RTKs</td>
<td>Acquired</td>
<td>R</td>
<td>2012</td>
<td>Ducan 2012</td>
</tr>
<tr>
<td>MEK2 Q60P, MEK2 C125S V35M and L46F and N126D</td>
<td>Acquired</td>
<td>R</td>
<td>ERKi</td>
<td>2009</td>
</tr>
<tr>
<td>BRAFp61</td>
<td>Acquired</td>
<td>R</td>
<td>2011</td>
<td>Polikakos</td>
</tr>
<tr>
<td>BRAF amplif</td>
<td>Acquired</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMURF2 (TGFB)</td>
<td></td>
<td>R</td>
<td>2013</td>
<td>Smith 2013</td>
</tr>
<tr>
<td>Notch overexpression</td>
<td>Intrinsic</td>
<td>R</td>
<td>Metformin</td>
<td>2008 2009</td>
</tr>
<tr>
<td>IGFR/IRS enhanced</td>
<td>Acquired</td>
<td>R</td>
<td></td>
<td>2012</td>
</tr>
<tr>
<td>concurrent loss of PTEN and Rb1</td>
<td>Intrinsic</td>
<td>R</td>
<td></td>
<td>2012</td>
</tr>
</tbody>
</table>
Immunologic Effects
MEKi suppress alloreactivity and graft-versus-host disease in a memory stage dependent manner

- Selumetinib preferentially (only in T naive cells)
  - inhibit alloreactivity T cells
  - inhibited cytokine production
  - inhibited alloreactivity mediated by naive and central memory CD4+ and CD8+ T cells
  - But relative sparing of progressively differenciated T cells (for HV and EBV)

Immunotherapy in multiple myeloma

Restoring function of monocyte derived dendritic cells by activating MEK/ERK pathway (by p38 –MAPK- inhibition)

Signaling pathways in the differentiating MoDCs obtained from healthy donors or myeloma patients.

MEKi vs BRAFi

Dabra did not affect function of Lymphocites
Trame or combination suppressed T-lymphocites proliferation, cytokine production and Ag specific expansion
Trame reduces DC viability
MEKi reduces ability of DCs to induce T cell proliferation

No data about checkpoint expression after MEKi

Laura J Vella. Cancer Immunology Research 2014
Ott. Cancer Immunotherapy 2013
MAPK pathway inhibition may have favorable effect on melanoma specific immune response.

Cooper 2013 Oncoimmunology
Sumimoto
Rebiopsies at 14 days: 16 patients treated with BRAFi or BRAF+MEK

- Increase expression of:
  - PDL1, TIM3, Ag melanoma (MART1, Tyr, GP100)
  - CD8T infiltrates (immunohistochemistry)
  - T cell markers of activation cytotoxic (perforin and granzyme) and T cell exhaustion (TIM3, PD1)

Decrease IL6, IL8

At progression: decrease Ag expression decreased and CD8 T cell infiltrate was abrogated (MAPK reactivation is responsible of re-establishment of an immunosuppressive tumor microenvironment)

BRAFi promotes T cell infiltration and increase melanoma antigen expression, however the immune response may be limited due to an increased in EXHAUSTION MARKERS on T cells and increase in PDL1

Frederick DT. CCR 2013
Effect of MEK inhibitors on melanoma antigen expression and activated ERK levels

Kono M et al. Mol Cancer Res 2006;4:779-792
Increased DC function upon MAPK pathway blockade in the tumor microenvironment.
Proposed signaling mechanism for c-Jun and STAT3 influence on PD-L1 expression in BRAFi-resistant
Conclusions

- MEK is not a worse drug than BRAF
- MEKi have their own indications in BRAF, NRAS, uveal, BRAF fussion melanoma
- Immunosupressive effects could be overcome by the activity, reversing immunosupresion due to cancer
- Immunotherapy in patients responding to inhibitors, probably better than patients in progression