Mechanisms of Resistance to BRAF/MEK Inhibitors
How to overcome them

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June 2016
GEM
Summary

1. Pathway
2. Different responders
   1. Long responders (15-20%): CR-----------------------------BRAFi+MEKi
   2. Refractory patients (5-10%): Intrinsic resistance----Immunotherapy, novel drugs
3. Resistance (80%): adaptative and acquired
   3.1. Heterogeneity: ----------------------Targeted drugs at progression: cfDNA,
       Novel combinations 1st line
       Novel drugs
   3.2. Adaptative resistance--------------------------On/off schedule
Main pathways in BRAF mutant melanoma

Karachaliou et al. ATM 2016
1. Long term survival Dabra + Trame

![Graphs showing long-term survival data for Dabra + Trame.]

**Table 2.** Baseline Characteristics, Best Response, and OS in Patients Treated With a Combination of Dabrafenib 150 mg Twice Daily and Trametinib 2 mg Once Daily: Part C (n = 54)

<table>
<thead>
<tr>
<th>Factor</th>
<th>No.</th>
<th>HR</th>
<th>Median OS, Months</th>
<th>1-Year OS, %</th>
<th>2-Year OS, %</th>
<th>3-Year OS, %</th>
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</thead>
<tbody>
<tr>
<td>RECIST best response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>13</td>
<td>0.98 (0.44 to 2.19)</td>
<td>21.3 (8.6 to not reached)</td>
<td>69 (37.3 to 87.2)</td>
<td>35 (10.9 to 60.2)</td>
<td>35 (10.9 to 60.2)</td>
</tr>
<tr>
<td>Partial response</td>
<td>33</td>
<td>0.38 (0.12 to 1.25)</td>
<td>23.1 (16.2 to 34.3)</td>
<td>79 (60.6 to 89.3)</td>
<td>48 (30.8 to 64.1)</td>
<td>33 (18.2 to 49.3)</td>
</tr>
<tr>
<td>Complete response</td>
<td>8</td>
<td></td>
<td>(29.0 to not reached)</td>
<td>100</td>
<td>88 (38.7 to 98.1)</td>
<td>63 (22.9 to 86.1)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

Long et al, JCO. Jan, 2016. DOI: 10.1200/JCO.2015.62.9345
PFS and OS by Best Response

**Progression-Free Survival**

- **1-yr**
  - Complete Response (CR): 90%
  - Partial Response (PR): 51%
  - Stable Disease (SD): 29%
  - Progressive Disease (PD): 68%

- **2-yr**
  - Complete Response (CR): 68%
  - Partial Response (PR): 51%
  - Stable Disease (SD): 29%
  - Progressive Disease (PD): 68%

**Overall Survival**

- **1-yr**
  - Complete Response (CR): 95%
  - Partial Response (PR): 83%
  - Stable Disease (SD): 55%

- **2-yr**
  - Complete Response (CR): 88%
  - Partial Response (PR): 55%

**No. at risk**

- Complete Response (CR): 100, 94, 52, 5
- Partial Response (PR): 316, 255, 107, 11
- Stable Disease (SD): 150, 68, 24, 4
- Progressive Disease (PD): 35, 13, 2, 0
- Not Evaluable (NE): 16, 1, 1, 0

PRESENTED BY GV LONG AT SMR 2015
Five Baseline Factors Influenced OS

LDH Normal

- N = 398
- 1Y = 85%
- 2Y = 67%
- 3Y = 57%

LDH ≥ ULN

- N = 219
- 1Y = 54%
- 2Y = 25%
- 3Y = 7%

Disease Sites < 3

- N = 237
- 1Y = 90%
- 2Y = 75%
- 3Y = 70%

Disease Sites ≥ 3

- N = 161
- 1Y = 76%
- 2Y = 55%
- 3Y = 38%

LDH >1-2 × ULN

- N = 149
- 1Y = 60%
- 2Y = 33%
- 3Y = 9%

LDH ≥ 2 × ULN

- N = 70
- 1Y = 40%
- 2Y = 7%
- 3Y = 7%

ECOG =

- N = 93
- 1Y = 71%
- 2Y = 43%
- 3Y = NE

ECOG ≥ 1

- N = 56
- 1Y = 42%
- 2Y = 19%
- 3Y = 16%

* Regression tree analysis.
NE, not estimable.
Long survivors with BRAFi: only BRAF mutations on WES

Wheler. BMC Cancer 2015
Ongoing Response in BRAF V600E-Mutant Melanoma After Cessation of Intermittent Vemurafenib Therapy: A Case Report

Andrew J. Dooley² · Avinash Gupta¹ · Mark R. Middleton¹

Dooley et al. Targ Oncol 2016

Gonzalez-Cao, BoadaA et al. Oncotarget In press
## 2. BRAFi Resistant Mechanisms: intrinsic resistance

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>Primary/acquired</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>NRAS mut</td>
<td>15</td>
<td>P/A</td>
<td>Mek+simvastatin, Meki+CDK4i, MEKi+EGFRi, MEKi+abt263, simvastatin+flavopiridol, simvastatin+CDK4i, MEKi+PI3Ki PLX7904, ERKi MEKi+nefinavir</td>
</tr>
<tr>
<td>BRAF FUSION</td>
<td>2</td>
<td>P</td>
<td>MEKi</td>
</tr>
<tr>
<td>MEK mut (NO P162S)</td>
<td>15</td>
<td>A/P</td>
<td>ERKi (SCH7729 MERK)</td>
</tr>
<tr>
<td>NF</td>
<td>2</td>
<td>A/P</td>
<td>MEKi+MTORi, CRAFi+BRAFi, panRAFi (AZ628), ERKi</td>
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<tr>
<td>COT sobre</td>
<td>?</td>
<td>A/P</td>
<td>-</td>
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<td>RAC1</td>
<td>3/14</td>
<td>P</td>
<td>PAKi</td>
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<td>MELP124</td>
<td>10/134</td>
<td>P</td>
<td>MEKi, ERKi</td>
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<tr>
<td>EGFR, pdgfr</td>
<td>6/16</td>
<td>A/P</td>
<td>Dasatinib, AKTi+EGFRi, (?) braf+pi3ki Holidays, HSP90i</td>
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<tr>
<td>HGF</td>
<td>?</td>
<td>P</td>
<td>BRAFi+METi, BRAFi+AKTi</td>
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<tr>
<td>PTEN loss, or RB inact</td>
<td>10-30</td>
<td>P/A</td>
<td>BRAFi+everolimus</td>
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<tr>
<td>ERB2, ERB3</td>
<td>?</td>
<td>A/P</td>
<td>BRAFi+Lapa ¿?</td>
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<tr>
<td>MED12</td>
<td>?</td>
<td>Mediator A</td>
<td>BRAFi+TGFBi (YR-290)</td>
</tr>
<tr>
<td>BCL2A1-MITF</td>
<td>?</td>
<td>A(P)</td>
<td>R to ERKi, BRAFi, MEKi; S BRAFi+bcla2i, obatoclax; Antiretroviral drugs</td>
</tr>
</tbody>
</table>
PTEN deletion/mutant pretreatment in BRAFi

Hartsough J Invest Dermatol 2013, Shi CCR 2013
Addition of Cobimetinib to Vemurafenib Overcomes the Negative Impact of *PTEN* Loss on PFS

PTEN+: H score ≥50

PTEN loss: H score <50

HR 0.36 (95% CI, 0.19-0.65) For PTEN loss Vem + Cobi vs. Vem

McArthur. ECCO 2015
TORC1 suppression increases the apoptotic response in BRAF-mutant melanomas

AZD8055 (mTORC inhibitor), GDC0941 (pan-PI3K inhibitor), BEZ235 (dual PI3K-TORC inhibitor), ABT-263 (BH3 mimetic)

P-S6 measurement can effectively identify tumors with ERK-independent resistance. Combinations of RAF inhibitor with a TORC inhibitor, a PI3K inhibitor, or a BH3 mimetic, may be effective.

Corcoran et al. STM 2013
Clinical trials using mTOR inhibition

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mec</th>
<th>Combination</th>
<th>Status</th>
<th>Nº</th>
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</thead>
<tbody>
<tr>
<td>BEZ235</td>
<td>DUAL pi3k/torc</td>
<td>MEKi</td>
<td>Completed</td>
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<tr>
<td>everolimus</td>
<td>mTOR</td>
<td>several</td>
<td>Completed without published results</td>
<td></td>
</tr>
<tr>
<td>AZD8055</td>
<td>mTOR</td>
<td></td>
<td>Completed</td>
<td></td>
</tr>
<tr>
<td>ABT-263 (navitoclax)</td>
<td>BH3 mimetic combination</td>
<td></td>
<td>Ongoing</td>
<td>NCT0189585</td>
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</table>
NF1 critically regulates KRAS and HRAS in melanomas

*NF1* was mutated in 38.7% of non *BRAF/NRAS* melanomas (29/75) and in ∼70% of non *BRAF/NRAS* samples with a UV-signature.
NF1 loss

16/121 melanomas harbored a NF1 missense or nonsense mutation. But clinically resistance has been only demonstrated in one patient that had it in the initial biopsy and had a short PFS.

Sensitive to pan-RAF inhibitor AZ628, the ERK inhibitor VTX11e, and the combination of a MEK + mTOR inhibitor (PD0325901 and rapamycin).

Gibney G T, Cancer Discovery 2013; Maertena, Cancer Discov 2013
Whole-exome sequencing identifies NF1 mutations in tumors of melanoma patients exhibiting resistance to vemurafenib

A

<table>
<thead>
<tr>
<th>Patient</th>
<th>PFS (mo)</th>
<th>Resistance</th>
<th>cDNA</th>
<th>Protein</th>
<th>Candidate splice motif</th>
<th>Splice motif sequence</th>
<th>Site broken?</th>
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<tbody>
<tr>
<td>15</td>
<td>1.5</td>
<td>De novo</td>
<td>c.135C&gt;T</td>
<td>p.N45N</td>
<td>Enhancer</td>
<td>ATCAAT</td>
<td>Yes</td>
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<tr>
<td>45</td>
<td>5</td>
<td>Acquired</td>
<td>c.4023G&gt;A</td>
<td>p.Q1341Q</td>
<td>Splice site</td>
<td>AACCTCCTTCAGAT</td>
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<td>46</td>
<td>2.5</td>
<td>De novo</td>
<td>c.7248C&gt;T</td>
<td>p.R2450*</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>50</td>
<td>2</td>
<td>De novo</td>
<td>c.3018C&gt;T</td>
<td>p.V1006V</td>
<td>Enhancer</td>
<td>ATGGTC</td>
<td>Yes</td>
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</table>

B

C

NF1 melanoma: growth responses to selumetinib and ERKi SCH772984

Krauthammer. Nat Genetics 2015
Clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mec</th>
<th>Combination</th>
<th>Status</th>
<th>Nº</th>
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<tbody>
<tr>
<td>LXH254 (Nov)</td>
<td>PanRAF</td>
<td>-</td>
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<tr>
<td>MLN2480</td>
<td>PanRAF</td>
<td>-</td>
<td>Ongoing</td>
<td>NCT02327169, NCT01425008 (melanoma)</td>
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<td>AZD628</td>
<td>PanRAF</td>
<td>-</td>
<td>preclinical</td>
<td></td>
</tr>
<tr>
<td>VTX11e</td>
<td>ERKi</td>
<td>-</td>
<td>preclinical</td>
<td></td>
</tr>
<tr>
<td>everolimus</td>
<td>mTOR</td>
<td>several</td>
<td>Completed without published results</td>
<td></td>
</tr>
</tbody>
</table>
Stroma
β-catenin-LEF1 and YAP1 signaling antagonistically co-regulate the tumor cell-intrinsic, apoptotic threshold of melanoma to MAPKi.
HGF from stromal cells: poor response

- Stromal cell lines secrete HGF in co-culture with BRAFmut cell lines
- Innate resistance
- BRAFi+METi

*Straussman Nature 2012*
# Clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Combination</th>
<th>Status</th>
<th>Nº</th>
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<tr>
<td>INC280 (Nov)</td>
<td>cMETi</td>
<td>BRAFi/MEKi</td>
<td>Ongoing</td>
<td>Logic2</td>
</tr>
</tbody>
</table>
Macrophage derived TNF: MITF upregulation

MITF target BCL2A1 has been shown to antagonize BRAF inhibition

Smith et al. Cancer Discov 2014
Acquired MITF amplification: resistance to BRAFi, MEKi and ERKi

Amplifications

![Bar chart showing amplifications of various genes with significance markers.](CGAN. Cell 2015)
Drug repositioning identifies nelfinavir mesylate as a suppressor of MITF expression

PAX3-mediated overexpression of MITF as a reversible resistance mechanism to MAPK-pathway
Intrinsically resistant cells showed diminished MITF expression and MITF transcriptional activity (as measured by levels of MITF target genes *TYRP1*, *MLANA*, and *PMEL*; 4/4 lines) and increase of AXL expression (2/4 lines). *Intrinsic resistance is not simply related to AXL expression.*
Low MITF/AXL ratio predict early resistance to ERK inhibition

- MITF low/AXL high is common in BRAF and NRAS melanomas
- MITF low in naive melanoma predict high resistance
- Also Mitf low in some melanomas with acquired resistance:
  - they must be treated with **AXLi combined with MAPKi**

Konieczkowski et al. Cancer Discov 2014

Mullerl et al. Nat Commun 2014
Clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mec</th>
<th>Combination</th>
<th>Status</th>
<th>Nº</th>
</tr>
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<tbody>
<tr>
<td>BMS345541</td>
<td>IKKi</td>
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<td>preclinical</td>
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<td>cabozantinib</td>
<td>AXLi</td>
<td>-</td>
<td>No trials in cutaneous melanoma</td>
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<td>Foretinib (GSK1363089)</td>
<td>AXL/METi</td>
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<td>BMS777607</td>
<td>AXLi</td>
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<tr>
<td>Bosutinib (SKI606)</td>
<td>AXLi</td>
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<td>preclinical</td>
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<tr>
<td>MGCD265 MGCD516</td>
<td>AXLi</td>
<td></td>
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<td>Nelfinavir</td>
<td>PI3Ki/Radisens</td>
<td>RT/TMZ</td>
<td>Ongoing GBM/NSCLC</td>
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</table>
3. Acquired resistance

Shi H. Cancer Discovery 2013 Nov
## 3. Acquired resistance

<table>
<thead>
<tr>
<th></th>
<th>%</th>
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<th>Treatment</th>
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</tr>
<tr>
<td>Braf ampl</td>
<td>15</td>
<td>A</td>
<td>BRAFi intermitente, Dosis de braf mayor, ERKi</td>
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<tr>
<td>Splicing</td>
<td>20</td>
<td>A</td>
<td>ERKi+ BRAFi, drug holidays, higher doses of BRAFi or MEKi, PLX7004</td>
</tr>
<tr>
<td>MEK mut (NO P162S)</td>
<td>15</td>
<td>A/P</td>
<td>ERKi (SCH7729 MERK)</td>
</tr>
<tr>
<td>NF</td>
<td>2</td>
<td>A/P</td>
<td>MEKi+MTORi, CRAFi+BRAFi, panRAFi (AZ628), ERKi</td>
</tr>
<tr>
<td>COT sobre</td>
<td>?</td>
<td>A/P</td>
<td></td>
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<tr>
<td>IGFR,</td>
<td>4/11</td>
<td>A</td>
<td>MEKi+IGFRi, BRAFi+IGFRi, MEKi+ AKTi or mtori or pi3ki, HSP90i</td>
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<tr>
<td>EGFR, pdgfr</td>
<td>6/16</td>
<td>A/P</td>
<td>Dasatinib, AKTi+EGFRi, (?), braf+pi3ki Holidays, HSP90i</td>
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<tr>
<td>FGFR3</td>
<td>?</td>
<td>A</td>
<td>MEK+FGFRi</td>
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<tr>
<td>PTEN loss, or RB inact</td>
<td>10-30</td>
<td>P/A</td>
<td>BRAFi+everolimu, BRAFi+PI3Ki</td>
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<td>ERB2, ERB3</td>
<td>?</td>
<td>A/P</td>
<td>BRAFi+Lapa ¿?</td>
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<td>MED12</td>
<td>?</td>
<td>Mediator A</td>
<td>BRAFi+TGFBi (YR-290)</td>
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<td>BCL2A1-MITF</td>
<td>?</td>
<td>A/P</td>
<td>R to ERKi, BRAFi, MEKi; S BRAFi+bcla2i, obatoclax</td>
</tr>
</tbody>
</table>
LGX818, MEK162, BKM120, BGJ398, INC280, LEE011 (LOGIC 2)

**Part I**
- Group A: BRAF and MEK naive
- Biopsy
- Optional LGX818/MEK162 combination
- Biopsy at PD
- Gen. Ass. and/or Run-in

**Part II**
- Optional LGX818/MEK162 combination
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)
- Optional LGX818/MEK162 combination
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)
- Optional LGX818/MEK162 combination
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)
- Optional LGX818/MEK162 combination
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)

**Group B**
- Any BRAF/MEK combination or single agents*
- Biopsy at PD
- Run-in**
- LGX818/MEK162 (first scan after 3 weeks)
- Genetic Assessment (Biopsy Analysis)
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)

**Group C**
- Columbus, LOGIC1, CMEK162X2110: LGX818/MEK162 arm
- Biopsy at PD
- Optional LGX818/MEK162 combination
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)
- Optional LGX818/MEK162 combination
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)
- Optional LGX818/MEK162 combination
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)
- Optional LGX818/MEK162 combination
- Biopsy at PD
- Genetic Assessment (Biopsy Analysis)
Heterogeneity intratumoral/intrapatient

Shi H et al. Cancer Discovery 2014; Wilmott 2012; Van Allen 2014; Romano 2014; Turajlic 2014
BRAF/MEK acquired resistance: how to overcome it?

3.1. Identification of the most relevant mechanism of resistance: cfDNA analysis
3.2. Triple combinations in first line setting: trying to improve PFS
3.3. Delayed adaptive resistance: on/off Schedule, other combinations?
3.4. Using at progression drugs with a broader spectrum of inhibition
3.1 cfDNA as a tool for selecting the targeted drug

BRAFi+MEKi

Gonzalez-Cao 2015
ctDNA can be used to monitor patient response

Maria Romina Girotti et al. Cancer Discov 2016;6:286
cfDNA next-generation sequencing in MOSCATO trial

COMBI-d: CDKN2A Loss in the Dabrafenib + Trametinib Arm

- **PFS**
  - CDKN2A WT (n = 45)
  - CDKN2A Mut (n = 18)
  - 3-y PFS, 27%
  - 3-y PFS, 8%

- **OS**
  - CDKN2A WT (n = 45)
  - CDKN2A Mut (n = 18)
  - 3-y OS, 55%
  - 3-y OS, 24%

* Cox proportional hazards P value; +, censored.

- **CDKN2A** mutation and deletion were significantly associated with poorer OS ($P = 0.027^a$) and PFS ($P < 0.001^a$)
- Preclinical data suggest that combination with CDK4/6 inhibitors could be a beneficial strategy

Presented By Keith Flaherty at 2016 ASCO Annual Meeting
NRAS treatment:
PD-0332991(CDk4/6i)+GSK 1120212(MEKi)

CR in 33% of mice


| Huang\(^1\) | Simvast+Falvop/MEKi |
| Kwong\(^2\) | MEKi+CDK4i |
| Corcoran\(^3\) | MEKi+abt-263 (bcl-xli) |
| Posch\(^4\) | MEKi+PI3Ki |
| Greger\(^5\) | MEKi+BRAFi+PI3Ki |
| Means-Powell\(^6\) | METi+Sorafenib |

1. Can Discovery 2013  
3. Cell 2013  
4. PNAS 2013  
5. Mol Cancer T 2012  
6. ASCO 2012

Nazarian. Nature 2010; McCarthur 2011; Ribas, JCO 2013; Van Allen, 2014
A phase 1b/2 study of LEE011 in combination with binimetinib (MEK162) in patients with NRAS-mutant melanoma

CDK4/6i (LEE011)+MEKi (MEK162)

OR 82% (N 22)

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>LEE011 + Binimetinib (N = 22)</th>
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</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Confirmed PR</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Unconfirmed PR</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>11 (50)*</td>
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<tr>
<td>Progressive disease</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Unable to evaluate</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>


Sosman. ASCO 2014, abs 9009
CHK1 inhibitors in RAS mutant cell lines

Morales D, Rosell R et al. ASCO 2016
## Clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mec</th>
<th>Combination</th>
<th>Status</th>
<th>Nº</th>
</tr>
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<tbody>
<tr>
<td>LEE011</td>
<td>CDK4/6</td>
<td>BRAF/MEKi</td>
<td>Ongoing</td>
<td>2011-005875-17 LOGIC-2</td>
</tr>
<tr>
<td>Abemaciclib (LY2835219)</td>
<td>CDK4/6</td>
<td>single</td>
<td>Ongoing Phase II</td>
<td>NCT02308020</td>
</tr>
<tr>
<td>SAR245409</td>
<td>PI3Ki/mTORi</td>
<td>pimasertib</td>
<td>Completed 2011</td>
<td>NCT01390818</td>
</tr>
<tr>
<td>BKM120</td>
<td>PI3Ki</td>
<td>BRAFi</td>
<td>Unknown 2013</td>
<td>NCT01512251</td>
</tr>
</tbody>
</table>
Splicing forms p61BRAFV600

- **6/19** patients: 61kd variant form of BRAF(V600E) that lacks exons 4-8, a region
- It could be sensible to higher dose or combination, unless it is also observed in pts with combined treatment (Hartsough et al., 2014)

Poulikakos P. Nature 2011
Whole exome sequencing identified $B-RAF^{V600E}$ amplification

4/20 patients

In vitro testing: growth inhibition could be achieved with higher dose of BRAFi

MEK1/2 mutations

- MEK1<sup>P124</sup> mutations co-occur at low frequency (~7%) with BRAF<sup>V600</sup> mutations. Pre therapy MEK1 codon 124 6/87; OR 2/6 (Sosman 2012)
- MEK1Q56P (1 pts to BRAFi) (Trunzer, 2013).
- MEK1P162S (1/5 pts): no gives resistance
- MEK1 mutation at progression 3/20 cases: sensituve t combination
- MEK2 Q60P (1/5 pts): resit combination but sensible to ERKi (Wagle, 2014)
- MEK2 C125S (R to BRAFi and MEki);
- MEK2 V35M and L46F and N126D (also resistance to BRAFi or MEKi, but no so intense as C125S (Van Allen 2014)

Wagle N et al. Cancer Discovery 2014
**AKT1 mut (Q79K)**

**Acquired** resistance to BRAFi in PTEN wild type

**Adaptative** resistance: early rebound of AKT pathway in wild PTEN null or PTEN wild but AKT mutant

Early rebound of PDGFRB (not EGFR) and downregulation of MYC (adaptative AKT signalling)

In melanomas without early adaptative AKT upregulation is more frequent late resistance by AKT than in melanomas with early AKT rebound

Shi H, Ribas et al C Discovery 2014:4: 69
SOX10 TGFB signaling increases EGFR and PDGFRB expression

IGF-1R, EGFR, erb2, erb3, PDGF

Villanueva. Cancer Cell 2010
Gopal, CR 2010
3.3. BRAF/MEK adaptative resistance: on/off schedule

Back up information

Discontinuous dosing strategy attenuates continued dependency on BRAF (V600E)-MEK-ERK signaling in resistant tumors, akin to reintroducing EGFR TKIs in EGFR mutant NSCLCs following chemotherapy. 

(Sequist et al. Science Trans Med 2011) (Chmielecki 2011)

Das Thakur et al. Nature 2013
Intermittent Vemurafenib (iBRAF) + Cobimetinib (iMEK): GEM-01-15

Objetivo principal:
- SLP

Objetivos secundarios
- Tasa de respuesta
- SLP 1 año, SLP 2 años
- SG, SG 1 año, SG 2 años
- Seguridad
- cfDNA BRAF V600 subestudio biomarcadores

Vemurafenib (960mg BID oral 1-28d) (ROCHE)
Cobimetinib (60mg QD oral 1-21d) (ROCHE)

Justificación
- Optimizar esquema de tratamiento V-C
- Retrasar resistencias
- Reducir perfil de seguridad
- Reducir coste tratamiento/mes
Reduced Proteolytic Shedding of Receptor Tyrosine Kinases Is a Post-Translational Mechanism of Kinase Inhibitor Resistance

Miles A. Miller et al. Cancer Discov 2016;6:382-399
Gonzalez Cao M et al. ATM 2015
Conclusions

- Resistance to BRAF inhibitors is mediated by different mechanisms.
  - Secondary NRAS mutations
  - Upregulation of RTKs (PDGFRβ, IGF1R, AXL)
  - BRAF truncations or amplification

- Adaptative resistance
  - On-off schedule

- Heterogeneous
  - Target key signaling node: ERKi, pan RAFi
  - Methods for looking at the most prevalent resistant mechanism: cfDNA