Dr. Elena Elez
Vall d’Hebron Institute of Oncology (VHIO)

21 junio 2017. Hospital Universitario Miguel Servet. Zaragoza
22 - 24 junio 2017. Hotel Villa de Sallent. Formigal
BRAF MUTANT TUMORS:  
New Evidence And Progress Expectatives

Elena Elez MD, PhD  
Gastrointestinal Cancer Unit  
Developmental Therapeutics Program  
meelez@vhio.net
NEW PARADIGMS

- Diagnosis, classification, and management of cancer are traditionally dictated by the site of tumor origin and specific histologic subtypes of site-of-origin cancers.

- Novel technologies allow rapid and accurate sequencing of clinical samples.

- New observations suggest an approach to the diagnosis and treatment of cancer driven by the unique molecular features of the tumor.

Turski et al. Mol Cancer Therap 2016
Few therapeutic options combined to treat tumors:
- Surgery
- Radiotherapy
- Few chemotherapies

Increase on therapeutic options allowed specific treatments for different tumor types:
- Combined chemo-radiation
- Specific protocols (guidelines)

Targeted agents that work in specific molecular alterations:
- Broad knowledge of molecular tumor biology
- Development of molecular analysis and targeted therapies
• Basket trials include patients with a wide variety of histologies as long as they all harbor a cognate aberration. Often perceived as signal finding.


The “Basket trial” is the paradigm of this approach
**SOME “STATS”**

*BRAF* is mutated in about 15% of all cancers\(^1,2\)

Found in solid tumors, hematologic malignancies, and related disease types.

For some cancers, *BRAF* mutations are very frequently detected: melanoma (40%–60% of patients) and hairy cell leukemia\(^3,4\).

<table>
<thead>
<tr>
<th>Cancer</th>
<th>BRAF mutation frequency</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholangiocarcinoma</td>
<td>3%-22%</td>
<td>Goepert et al (33)</td>
<td><em>BRAF V600E (60%)</em>, <em>BRAF V600D (13%)</em>, Other codons (27%)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>2.8%</td>
<td>Jebaraj et al (95)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5%-15%</td>
<td>Pekinshah et al (96)</td>
<td></td>
</tr>
<tr>
<td>MSI unstable</td>
<td>27.8%-51.8%</td>
<td>Domingo et al (97)</td>
<td></td>
</tr>
<tr>
<td>MSI stable</td>
<td>5%-7.5%</td>
<td>Samovitz et al (98)</td>
<td></td>
</tr>
<tr>
<td>Erdheim-Chester disease</td>
<td>54%</td>
<td>Haroche et al (100)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>43%</td>
<td>Gupta et al (101)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>GIST</td>
<td>2%-13%</td>
<td>Hostin et al (102)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>1.7%</td>
<td>Sakata-Yanagimoto (104)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>100%</td>
<td>Tiacci et al (13)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>3%</td>
<td>COSMIC (23)</td>
<td><em>BRAF V600E (85%)</em>, Other codons (5%)</td>
</tr>
<tr>
<td>Lung cancer adenocarcinoma</td>
<td>3%</td>
<td>Cooper et al (103)</td>
<td><em>BRAF V600E (50%)</em>, <em>BRAF G469A (39%)</em>, <em>BRAF D594G (11%)</em></td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>25%-38%</td>
<td>Go et al (107)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>Melanoma</td>
<td>60%</td>
<td>Haroche et al (100)</td>
<td><em>BRAF V600E (80%)</em>, <em>BRAF V600K (8%)</em>, <em>BRAF V600R (1%)</em>, Other codons (10%)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>6%</td>
<td>Lohr et al (109)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>35%-60%</td>
<td>Grisham et al (110)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>Serous borderline cancer</td>
<td>44.6%-77%</td>
<td>Bosmiller et al (111)</td>
<td></td>
</tr>
<tr>
<td>Low-grade serous carcinoma</td>
<td>5.3%-14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1%-16%</td>
<td>Schultz et al (112)</td>
<td><em>BRAF V600E</em></td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>70%-90%</td>
<td>Karshunov et al (28)</td>
<td><em>BRAF-KIAA1549 fusion</em></td>
</tr>
<tr>
<td>Pleomorphic xanthoastrocytoma</td>
<td>66%</td>
<td>Schindler et al (113)</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary thyroid cancer</td>
<td>30%-80%</td>
<td>Xing (114)</td>
<td></td>
</tr>
</tbody>
</table>

*Multiple other tumors may have a small incidence of *BRAF* mutations not described here. Additionally some tumors may have *BRAF* amplification or fusions as noted in the comments column or as discussed in the section entitled “Abnormalities in the *BRAF* gene other than Mutations.”

SOME BIOLOGY

- Predominant mutation: V600E (70-90%)
- Substitution of glutamic acid for valine affects activation mimicking the phosphorylation of the kinase domain, causing a change in structure that favors the active conformation.

- BRAF V600E mutations are activating with an increased kinase activity, activation of downstream effectors and oncogenic transformation

- Other activating mutations:
  - BRAF V600K 7%-19% (in melanoma)
  - Other: BRAF V600D (0.1%), V600R (1%), V600M (0.3%), L597 substitutions (0.5%), and K601E (0.7%).

- Inactivating or "low-activity MT typically involve substitutions at codon 594.

- Other BRAF aberrations include amplification and fusions.
**BRAF AND COLON CANCER**

- Small population:
  - 8-10% early stage
  - 4-5% late stage
- BRAF V600E mutations as a biomarker?
  - Very poor prognosis in late stage (mCRC)
  - Predictive: negative predictive effect for anti-EGFR MoAbs in some studies:
    - Cetuximab: refractory (European cons.)\(^1,2\) & first-line setting (CRYSTAL study)\(^3\)
    - Panitumumab: 2\(^{nd}\) line setting (PICCOLO study)\(^4\)
    - No change in the label by any regulatory authority

---

\(^1\) Di Nicolantonio F, J Clin Oncol 2018; \(^2\) De Roock et al. Lancet Oncol 2010; \(^3\)Van Cutsem et al, J Clin Oncol 2011; \(^4\)Seymour MT et al, Proc ASCO 2011
The outcome of BRAF- mutation-positive patients treated with FOLFOXIRI plus bevacizumab (median overall survival 19 months; median progression-free survival 7·5 months; best response 56%)
STANDARD OF CARE AIMS IN mCRC

VELOUR trial biomarkers update: Impact of RAS, BRAF, and sidedness on afiblercept activity.

Data on 36 BRAF MT patients
EGFR signaling is inhibited by hyperactive BRAF. In the presence of BRAF inhibitor, EGFR signaling is reactivated either by the BRAF-MEK pathway or the PI3K-AKT pathway, resulting in cellular proliferation and survival.

Adapted from Van Geel et al. ASCO 2014
**BRAF INHIBITION**

**Phase IB Study of Vemurafenib in Combination with Irinotecan and Cetuximab in Patients with Metastatic Colorectal Cancer with BRAF^{V600E} Mutation**

David S. Hong1, Yee K. Norris1, Raed El Oce1, Alexander V. Sorokin2, Filip Janjic3, Sing-Ping1, Michael J. Overman4, Emeline Piber-Paul, Vivek Subbiah4, Bryan Kee4, Agostina M. Tumberdou1, David Fidler5, Jorge Bellm6, Imad Shibli2, Helen Huang3, Johnique Atkins4, Gabi Tercic6, Nicolas Sommer1, Richard Lammert5, Funds Marie-Bernstam1, and Scott Kopetz6

![Graph showing % Reduction by RECIST 1.1 with 35% RR]

- **Appendiceal cancer**
- **Colorectal cancer**
  - Prior cetuximab
  - Remains on study

**35% RR**

- Median PFS 7.7 months (95% CI, 3.2–NR)

Hong et al. Cancer Discov 2016
BRAF INHIBITION

SWOG 1406

Eligibility:
1) BRAF V600 mutation
2) Prior treatment for metastatic disease
3) No more than 2 prior progression on chemotherapy
4) No prior cetuximab

Stratified:
1) Prior treatment with irinotecan

Arm A
- Cetuximab + Irinotecan

Arm B
- Vemurafenib + Cetuximab + Irinotecan

Cetuximab + Irinotecan + Vemurafenib

Historical response rate is <10% for cetuximab and irinotecan, with PFS of 2.4 months for BRAF\textsuperscript{mut}

Target HR 0.5 for PFS, with 2-sided alpha 5%, power 90%
N = 105 patients
**BRAF INHIBITION**

**Primary Endpoint: Progression-free survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Median</th>
<th>95% Conf Int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + Irinotecan</td>
<td>50</td>
<td>48</td>
<td>2.0</td>
<td>(1.8 – 2.1)</td>
</tr>
<tr>
<td>Vemurafenib + Cetuximab + Irinotecan</td>
<td>49</td>
<td>40</td>
<td>4.3</td>
<td>(3.6 – 5.7)</td>
</tr>
</tbody>
</table>

HR = 0.48  
95% CI 0.31 – 0.75  
P = 0.001

**Response Rate**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cetuximab + Irinotecan</th>
<th>Vemurafenib + Cetuximab + Irinotecan</th>
<th>P-value³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response²</td>
<td>4%</td>
<td>16%</td>
<td>.001</td>
</tr>
<tr>
<td>Stable disease</td>
<td>17%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Progression³</td>
<td>66%</td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>

**Crossover to VIC after progression**

- Patients with radiographically documented progression on IC crossed over to receive VIC
- 48% of patients treated on IC arm crossed over

**Secondary Endpoint: Overall Survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Median</th>
<th>95% Conf Int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + Irinotecan</td>
<td>50</td>
<td>38</td>
<td>5.9</td>
<td>(3.0 – 9.9)</td>
</tr>
<tr>
<td>Vemurafenib + Cetuximab + Irinotecan</td>
<td>49</td>
<td>32</td>
<td>9.6</td>
<td>(7.5 – 13.1)</td>
</tr>
</tbody>
</table>

HR = 0.73  
95% CI 0.45 – 1.17  
P=0.19
## BRAF INHIBITION

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response rate</th>
<th>PFS</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single/Doublet BRAF/MEK</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>5%</td>
<td>2.1 months</td>
<td>Kopetz, ASCO ‘10</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>11%</td>
<td>NR</td>
<td>Falchook, Lancet ‘08</td>
</tr>
<tr>
<td>Encorafenib</td>
<td>16%</td>
<td>NR</td>
<td>Gomez-Roca, ESMO ‘14</td>
</tr>
<tr>
<td>Dabr +Tramet</td>
<td>12%</td>
<td>3.5 months</td>
<td>Corcoran, ASCO ‘14</td>
</tr>
<tr>
<td><strong>Doublet with EGFR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vem + Panit</td>
<td>13%</td>
<td>3.2 months</td>
<td>Yeager et al CCR ‘14</td>
</tr>
<tr>
<td>Vem + Cetux</td>
<td>20%</td>
<td>3.2 months</td>
<td>Tabernero et al ASCO ‘14</td>
</tr>
<tr>
<td>Encoraf + Cetux</td>
<td>22%</td>
<td>4.2 months</td>
<td>Tabernero et al ESMO GI 2016</td>
</tr>
<tr>
<td>Dabr + Panit</td>
<td>10%</td>
<td>3.5 months</td>
<td>Corcoran, ESMO 2016</td>
</tr>
<tr>
<td><strong>Triplet with EGFR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vem + Cetux + Irinotecan</td>
<td>16%</td>
<td>4.4 months</td>
<td>Kopetz et al, ASCO GI ‘17</td>
</tr>
<tr>
<td>Dabr + Tramet + Panit</td>
<td>21%</td>
<td>4.2 months</td>
<td>Corcoran, ESMO ‘16</td>
</tr>
<tr>
<td>Encoraf + Cetux + Alpelisib</td>
<td>27%</td>
<td>5.4 months</td>
<td>Tabernero et al ESMO GI ‘16</td>
</tr>
</tbody>
</table>
CLGX818X2103: BRAF INH + CETUXIMAB +/- PIK3CA INH

**Objective:** To evaluate the combination of encorafenib (ENCO; BRAF inhibitor) and cetuximab (CETUX; EGFR antibody) with or without alpelisib (ALP; PI3K inhibitor) in BRAFm CRC (ClinicalTrials.gov: NCT01719380)

**Phase 1b**
- Provided RPTDs for ENCO and ALP in the combination regimens
- Included patients (N=54) with BRAFm CRC failing ≥1 prior therapy

**Phase 2**
- Evaluated efficacy and safety of the triplet vs doublet regimen
  - Primary endpoint: PFS
  - Secondary endpoints: confirmed ORR, OS, safety & tolerability
- Included patients (N=102) with BRAFm CRC failing ≥1 prior therapy

**Triplet regimen**
- n=28
  - ENCO + ALP + CETUX
  - ENCO: 200 mg
  - ALP: 300 mg

**Doublet regimen**
- n=26
  - ENCO + CETUX
  - ENCO: 200 mg

**Randomized 1:1**
- Triplet regimen
  - n=52
  - ENCO 200 mg orally QD + ALP 300 mg orally QD + CETUX per label*

- Doublet regimen
  - n=50
  - ENCO 200 mg orally QD + CETUX per label*

---

ALP = alpelisib; BRAFm CRC = BRAF-mutant colorectal cancer; CETUX = cetuximab; EGFR = epidermal growth factor receptor; ENCO = encorafenib; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI3K = phosphatidylinositol 3-kinase; QD = once daily; RPTD = recommended phase 2 dose

* Intravenously dosed at 400 mg/m² for the first dose and 250 mg/m² for subsequent weekly doses

Tabernero et al. ESMO GI 2016
## BRAF INHIBITION

<table>
<thead>
<tr>
<th>Confirmed Response</th>
<th>ENCO + ALP + CETUX n=52</th>
<th>ENCO + CETUX n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Stable disease</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td><strong>Overall response rate, % (95% CI)</strong>*</td>
<td>27 (16–41)</td>
<td>22 (12–36)</td>
</tr>
<tr>
<td><strong>Disease control rate, % (95% CI)</strong>*</td>
<td>85 (72–93)</td>
<td>84 (71–93)</td>
</tr>
<tr>
<td><strong>Median (95% CI) duration of response, mo</strong></td>
<td>9.9 (2.8–11.0)</td>
<td>4.6 (2.0–6.7)</td>
</tr>
</tbody>
</table>

Tabernero et al. ESMO GI 2016
**BRAF INHIBITION**

**Primary Endpoint:** Overall survival (OS) of the triplet therapy compared to the control arm.

**Secondary Endpoints:** Address efficacy of the doublet therapy compared to the control arm, and the triplet therapy compared to the doublet therapy.

**Other Secondary Endpoints:** Progression-free survival (PFS), objective response rate (ORR), duration of response, safety and tolerability. Health related quality of life data will also be assessed.

The trial will be conducted at over 250 investigational sites in North America, South America, Europe and the Asia Pacific region. Patient enrollment is expected to be completed in 2018.
NEW APPROACHES

- **Non-specific Kinase Inh**
  - Sorafenib
  - Regorafenib

- **BRAFV600E specific**
  - Vemurafenib
  - Dabrafenib
  - Encorafenib (LGX818)
  - RAF265/CHIR265
  - BMS-908662/XL281 (GSK2118436)

- **2nd generation BRAFi**
  - PLX8394/PLX7904

- **RO5126766/CH5126766 (BRAF/MEKi)**

- **CCT196969, CCT241161**
  - LY3009120
  - ARQ-736
  - MLN2480

- **RAF265 (BRAF^G90E: VEGFR and RET)**

- **Inhibitors of membrane association**
  - Minival
  - FTIs
  - GGTIs
  - Deltarasin

- **Mutation Specific**
  - Direct KRAS inhibitor G12C

- **Targeting RAS at RNA level**
  - Anti-sense oligonucleotids siRNA

- **KRAS**

- **MAPKi**

- **MEKi**

- **ERKi**

- **MK8353**
  - GDC-0994
  - BVD523
  - SCH772984
  - VTX11e

- **E6201 (MEK/MEK1 inh)**

- **allosteric MEK1/2i**
  - Trametinib (GSK1210212)
  - Pimasertib (AS703026)
  - Selumetinib (AZD6244)
  - PD0325901
  - Refametinib (BAY86-9766)
  - TAK733
  - MEK162 (ARRY438162)
  - WX554
  - RO4987655
  - ARRY-300
  - AS703988
  - AZD8830
  - E6201

- **allosteric MEK1i**
  - Cobimetinib (GDC0973)

*Slide courtesy of Jordi Rodon*
NEW APPROACHES

**BRAF V600E** Mutant Colorectal Cancer Subtypes Based on Gene Expression
NEW APPROACHES
NEW APPROACHES

CMS1
MSI immune

- MSI, CIMP high, hypermutation
- BRAF mutations
- Immune infiltration and activation
- Worse survival after relapse

CMS4
Mesenchymal

- Stromal infiltration, TGF-β activation, angiogenesis
- Worse relapse-free and overall survival

Guinney et al. Nature Cancer 2015
NEW APPROACHES

A Vulnerability of a Subset of Colon Cancers with Potential Clinical Utility

- BRAF(V600E) mutant colon cancers have a characteristic gene expression signature that is also found in some tumors lacking this mutation
- *RANBP2* is essential for survival of BRAF-like
- *RANBP2* loss exacerbates the defective microtubules outgrowth in BRAF-like CC cells
- Vinorelbine is selectively toxic to BRAF-like colon cancer

Vecchione et al. Cell 2016
NEW APPROACHES

Molecularly guided Trials with treatment strategies in patients with advances newly molecular defined subtypes of Colorectal cancer

• To stratify CRC patients based on molecular signatures and match them to specific therapies
  • TGFβ gene signature
  • BRAFm-like gene signature
  • MSI like gene signature
BRAF MUTANT TUMORS:
New Evidence And Progress Expectatives
“NEW EVIDENCE”

• Testing for \textit{BRAF} mutation is standard of care

• Strong prognostic information:
  – Useful for clinical management
  – Indirect information from phase III mCRC pivotal trials
    • Avid or response tumors
    • Data must be interpreted with caution

• Patients with \textit{BRAF} mut CRC have distinct biology but is an heterogenous disease

• \textit{BRAF} mutant patients have options:
  – \textit{BRAF}+\textit{EGFR}+irinotecan appear promising
  – Triple combinations are proving efficacy
• Deeper knowledge is needed when talking about BRAF mutant CRC (arising data about signatures and resistance mechanisms to targeted therapy): “-omics” are needed

• Consider targeting this hit contextualizing with signatures:
  – CMS1: Immunotherapy studies may be particularly relevant for patients with \( \text{BRAF}^{\text{mut}} \) CRC
  – CMS4: 20% of the whole \( \text{BRAF}^{\text{mut}} \) patients (TGF\( \beta \) inh)
  – Consider \( \text{BRAF}^{\text{mut}} \)-like patients

PLEASE ENROLL PATIENTS IN CLINICAL TRIALS (we’ll try to do our best!): meelez@vhio.net
THANK YOU FOR YOUR ATTENTION

meelez@vhio.net

21 junio 2017. Hospital Universitario Miguel Servet. Zaragoza

22 - 24 junio 2017. Hotel Villa de Sallent. Formigal

La Comisión de Formación Continuada de Las Profesiones Sanitarias de Aragón acredita la actividad de:
Zaragoza con 0,2 créditos (nº exp. 02 0010 16 0003) | Formigal con 2,2 créditos (nº exp. 02 0010 16 0004)