CAN WE DO BETTER IN BRAF MUTANT CRC?

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**SOME BIOLOGY**

- **BRAF mutation**: Found in solid tumors, hematologic malignancies and related disease types (15% of all cancers).
- Predominant mutation: *V600E* (70-90%) 
- **BRAF** V600E mutations are activating with an increased kinase activity 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.
TREATING BRAF MUTANT TUMORS

- 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
COLON CANCER SCENARIO

• 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

• Non specific approved treatments:
  – TRIBE\(^5\) (29 BRAF Mt pts): mOS 19 m; PFS 7’5 m
  – VELOUR\(^6\) (36 BRAF MT pts): mOS 10’3 vs 5’5m; mPFS 5’5 vs 2’2m

BRAF INHIBITION IN mCRC

- <10% responses with braf inhibitors in monotherapy\(^1,2\)
- This poor response seem to provide evidence that biomarker driven approaches to the treatment of cancer is not enough unless taken with histologic context.

\(^1\) Kopetz S et al. J Clin Oncol 2015

<10% responses with braf inhibitors in monotherapy\(^1,2\)

This poor response seem to provide evidence that biomarker driven approaches to the treatment of cancer is not enough unless taken with histologic context.

\(^1\) Kopetz S et al. J Clin Oncol 2015
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\(^1,2\)

## 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/Doubllet 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>Taberner ro et al ASCO '14</td>
</tr>
<tr>
<td>Encoraf + Cetux</td>
<td>22%</td>
<td>4.2 months</td>
<td>Taberner ro 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>Taberner ro et al ESMO GI '16</td>
</tr>
</tbody>
</table>
Historical response rate is <10% for cetuximab and irinotecan with PFS of 2.4 months for the BRAF mt pts. Target HR 0.5 for PFS (m PFS 2.4 vs 4.8m).
Equal activity when analyzed per MSI status, PK3CA mutations, prior irinotecan or sidedness
Trend for a benefit in terms of OS (limited due to a high rate of crossover)
The increased suppression of MAPK signaling by D + P + T may be one explanation for increased efficacy.

Corcoran et al. ESMO 2016 (adapted)
TRIPLE INHIBITION

Triple MAPK Pathway Inhibition in BRAF-mutant CRC

MAPK Signaling in Colorectal Cancer

HT-29 BRAF\textsuperscript{V600E} colorectal xenografts

Each bar represents change in tumor volume in one animal at day 21. The control group showed increases in tumor size for all animals, with mean increase in tumor volume versus baseline of 285%.

1. Adapted From: Strickler JH. Cancer Treatment Reviews. 2017; 60:109-119

BINI=binimetinib.
BEACON TRIAL

BEACON CRC Phase 3 Study Design

Safety Lead-in Completed

- ENCO 300 mg QD
  + BINI 45 mg BID
  + CETUX 400 mg/m² (initial) then 250 mg/m² QW
  N=30

Phase 3 Currently Enrolling

- Triplet therapy
  ENCO + BINI + CETUX
  n=205

- Doublet Therapy
  ENCO + CETUX
  n=205

- Control Arm
  FOLFIRI + CETUX, or IR + CETUX
  n=205

Disease progression
Continued follow-up for evaluation of OS

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FOLFIRI=folinic acid, fluorouracil, and irinotecan hydrochloride; IR=irinotecan

Van Cutsem et al. ESMO GI 2018
## Safety Lead-in to the BEACON CRC Phase 3 Trial

### Eligible Patients

- **BRAF**$^{V_{600E}}$ mutant mCRC
- Progressed after 1 or 2 previous regimens
- ECOG PS of 0 or 1
- No prior treatment with any RAFi, MEKi, or EGFRi
- Prior treatment with irinotecan allowed
- Eligible to receive CETUX per local label

### Safety Lead-in

<table>
<thead>
<tr>
<th>ENCO + BINI + CETUX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=30</strong></td>
</tr>
</tbody>
</table>

- **Dose-determining cohort** n=9
- **Dose expansion cohort** n=21
## Baseline Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PATIENTS (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF^V600E</strong> mutation*</td>
<td>29 (97%)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Age, median (range), year</td>
<td>59 (38–77)</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>17 (57%)</td>
</tr>
<tr>
<td><strong>Location of primary tumor</strong></td>
<td></td>
</tr>
<tr>
<td>Right side</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>Left side</td>
<td>9 (30%)</td>
</tr>
<tr>
<td><strong>No. of organs with metastases, &gt;1</strong></td>
<td>22 (73%)</td>
</tr>
<tr>
<td><strong>Metastatic site locations</strong></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>15 (50%)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>Lung</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (50%)</td>
</tr>
<tr>
<td><strong>No. of prior systemic therapies†</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>2</td>
<td>13 (43%)</td>
</tr>
<tr>
<td><strong>Received prior irinotecan</strong></td>
<td></td>
</tr>
<tr>
<td>MSI-H†</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

*1 patient treated with a non-V600E BRAF mutation. †Includes prior systemic therapies in the metastatic setting only. ‡Based on immunohistochemical assessment of MLH1 and MSH6 proteins successfully analyzed in 23 patients.
**Confirmed Best Overall Response**

<table>
<thead>
<tr>
<th>CONFIRMED BEST OVERALL RESPONSE*</th>
<th>PATIENTS (N=29)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>14 (48%)</td>
</tr>
<tr>
<td></td>
<td>(95% CI 29%–67%)</td>
</tr>
<tr>
<td>CR</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable for response‡</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

- ORR for patients with 1 and 2 prior regimens were 62% and 31% respectively
- 43% of responders have response ≥6 months
- Median DOR: 5.5 mo (95% CI, 4.1–NR)

*Local assessed confirmed responses per RECIST 1.1
†Patients with BRAF^{V600E} mutations.
‡Non-responders per intent-to-treat analysis.

CR=complete response; DOR=duration of response; NR=not reached; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.
BEACON TRIAL

Best Percentage Change in Tumor Measurements from Baseline

*Patients with lymph node disease with decreases in short axis dimensions consistent with RECIST 1.1 defined Complete Response.

†One patient had no baseline sum of longest diameters and is not presented.
Best Percentage Change in Tumor Measurements from Baseline

*Patients with lymph node disease with decreases in short axis dimensions consistent with RECIST 1.1 defined Complete Response.

†One patient had no baseline sum of longest diameters and is not presented.

BEACON TRIAL

Progression-Free Survival

Median PFS (95% CI): 8.0 mo (5.6–9.3)

Patients with $BRAF^{V600}$ mutation (N=29)

Censored patients

Patients at risk

0 3 6 9 12 15
0 3 6 9 12 15

Van Cutsem et al. ESMO GI 2018
Overall Survival

Median OS: Not reached
Data fully mature through 12.6 months*

* All patients have either died or have follow-up through 12.6 months.
Overall Survival

1-year OS rate: 62%

Survival Rate | 1 Prior Regimen | 2 Prior Regimens
--- | --- | ---
6 mo | 88% | 85%
12 mo | 63% | 62%

Patients with BRAF V600 mutation (N=29)

Censored patients
Adverse Events* Regardless of Causality (N=30)

<table>
<thead>
<tr>
<th>EVENT</th>
<th>ANY GRADE</th>
<th>GRADE 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>23 (77%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>19 (63%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (63%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (63%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (50%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14 (47%)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (40%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12 (40%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (37%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Increased CK</td>
<td>11 (37%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 (33%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (33%)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (30%)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (27%)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>8 (27%)</td>
<td>0</td>
</tr>
<tr>
<td>Skin fissures</td>
<td>8 (27%)</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>8 (27%)</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>6 (20%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>PPED syndrome</td>
<td>6 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>6 (20%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*AEs occurring in ≥20% of patients
Aspartate aminotransferase=AST; CK=creatin phosphokinase. PPED=palmar-plantar erythrodysesthesia
Conclusions

- All efficacy outcomes (ORR, PFS and OS) for the ENCO + BINI + CETUX triplet showed substantial improvements over historical data and over updated results for the doublet of ENCO + CETUX in patients with $BRAF^{V600E}$ mCRC\(^1-5\)
  - OS data are fully mature through 12.6 mo and median OS was not reached
    - Observed 1-year OS rate was 62%
  - Median PFS was 8.0 mo and ORR was 48%; 43% of responses lasted $\geq$6 mo
- The triplet was well tolerated with no unexpected toxicities
- The phase 3 portion of the BEACON CRC trial has been initiated and enrollment is ongoing

In BEACON CRC SLI, ENCO + BINI + CETUX triplet combination showed promising safety and efficacy data in patients with $BRAF^{V600E}$ mCRC

MAPK pathway alterations have demonstrated to be important drivers of acquired resistance leading due to reactivation of MAPK signaling\(^1\).

Exome sequencing analyses of paired pretreatment and postprogression biopsies from “responder patients” to targeted therapy have identified potential explanations for resistance:

- **KRAS** mutations,
- **KRAS amplifications**
- **BRAF amplifications**
- **MEK mutations**

These alterations confer sustained MAPK pathway activation *in vitro* but retained sensitivity to an ERK inhibitor.
ACQUIRED RESISTANCE

Cancer Research

Molecular Landscape of Acquired Resistance to Targeted Therapy Combinations in *BRAF*-Mutant Colorectal Cancer

![Table and Diagram]

OVERCOMING RESISTANCE

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

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

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

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

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

**RAF265 (BRAF500E; VEGFR and RET)**

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

**Mutation Specific**
- Direct KRAS inhibitor G12C

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

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

**MAPKi**
- E6201 (MEK/MEKK1 inh)

**MEKi**
- Allosteric MEK1/2i
  - Trametinib (GSK1120212)
  - 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

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

- KRAS mut
  $n = 2,224$

- BRAF mut
  $n = 1,941$

- APC mut
  $n = 393$

- TP53 mut
  $n = 801$
mCRC dMMR/MSI-H per local laboratory, ≥ 1 prior line of therapy
Nivolumab 3 mg/kgQ2W

Responses observed regardless BRAF mutation status

Overman et al. ASCO GI 2017
NEW APPROACHES

MOTrICOLOR

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-LIKE TUMORS

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
Non-V600 BRAF Mutations Define a Clinically Distinct Molecular Subtype of Metastatic Colorectal Cancer

- 2.2% of 9,643 patients
- 22% of all BRAF mutations significantly younger patients, less females
- Low grade left sided tumors
- mOS significantly longer
- Multivariable analysis, non-V600BRAF mutation was independently associated with improved OS (HR, 0.18; p 0.001).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>BRAF V600E</th>
<th>BRAF Non-V600</th>
<th>BRAF WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>295 (60)</td>
<td>19 (19)</td>
<td>92 (63)</td>
<td>184 (74)</td>
</tr>
<tr>
<td>Right</td>
<td>198 (40)</td>
<td>80 (81)</td>
<td>53 (37)</td>
<td>65 (26)</td>
</tr>
<tr>
<td>Missing</td>
<td>97</td>
<td>34</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>RAS status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MT</td>
<td>179 (31)</td>
<td>3 (2)</td>
<td>51 (26)</td>
<td>125 (50)</td>
</tr>
<tr>
<td>WT</td>
<td>396 (69)</td>
<td>130 (98)</td>
<td>142 (74)</td>
<td>124 (50)</td>
</tr>
<tr>
<td>Missing</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>MSI status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (15)</td>
<td>13 (30)</td>
<td>6 (6)</td>
<td>14 (22)</td>
</tr>
<tr>
<td>No</td>
<td>181 (85)</td>
<td>31 (70)</td>
<td>99 (94)</td>
<td>51 (78)</td>
</tr>
<tr>
<td>Missing</td>
<td>376</td>
<td>89</td>
<td>103</td>
<td>184</td>
</tr>
</tbody>
</table>

Jones et al. J Clin Oncol 2017
CAN WE DO BETTER IN BRAF MUTANT CRC?
SUMMARY AND CONCLUSIONS

CAN WE DO BETTER IN BRAF MUTANT CRC?

1. BRAF mutational status matters in CRC?
   ✓

2. Must be BRAF tested upfront?
   ✓

3. Is BRAF a prognosis factor?
   ✓

4. Is BRAF a predictive factor for response?
   ✓

5. Do we have options in the already approved therapeutic armamentarium of CRC?
   ✓

6. Do we have specific targeted therapy for this population?

7. Are 1 to 6 enough?
   ✗
THANK YOU FOR YOUR ATTENTION

Elena Elez Md PhD
Colon Cancer Program
Vall d’Hebron Institute of Oncology (VHIO)