How to Approach the Patient with BRAF Mutant Tumor

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Disclosures

Advisory Board:
• Roche/Genentech, EMD Serono/Merck KGA, Karyopharm Therapeutics, Merck, Amal Therapeutics, Navire Pharma, Holy Stone, Symphogen, Biocartis, Amgen, Novartis, Lilly, Boehringer Ingelheim, Boston Biomedical, Pierre Fabre, AstraZeneca/Medimmune, Bayer Health

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“BRAF Mutations”: V600E and Atypical / Non-V600E mutations

- BRAF V600E: 7%
- Atypical or Non-V600 BRAF mutation: 4%
- BRAF wild type: 89%

Cbioportal; referencing Cancer Cell ‘18
“BRAF Mutations”: V600E and Atypical / Non-V600E mutations

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- BRAF wild type: 89%

Cbioportal; referencing Cancer Cell ‘18
## Guideline Recommendations: Test for BRAF V600E

<table>
<thead>
<tr>
<th></th>
<th>NCCN</th>
<th>ESMO</th>
<th>ESMO Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing</strong></td>
<td>All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and <strong>BRAF mutations</strong> individually or as part of a next-generation sequencing (NGS) panel.</td>
<td>Tumour <strong>BRAF mutation</strong> status should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment</td>
<td>Tumour <strong>BRAF mutation status</strong> (V600E) should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment</td>
</tr>
</tbody>
</table>

**BRAF^{V600E}** is associated with poor OS and atypical metastases

Increased incidence compared to BRAF wild type

Modest et al, Ann Onc ‘16

Morris et al, Clinical Colorectal Cancer ‘13
Population-based data suggests even high prevalence and worse outcomes for pts with $\text{BRAF}^{\text{V600E}}$ than academic series

Chu et al ASCO ‘19
RAS/BRAF testing: Barriers in dissemination of best-practices

Low rate of initial biomarker testing

Flat Iron Health: 13,437 patients with mCRC from 2013 to 2017, testing with 1st line therapy

Need for education/awareness

Median time to obtain testing results: 26 days

Florea et al GI ASCO ‘18
## Guideline Recommendations: BRAF mutation (V600E)

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<tbody>
<tr>
<td><strong>EGFR antibody use</strong></td>
<td>Cetuximab or panitumumab based chemotherapy combinations are only recommended with KRAS/NRAS/BRAF wild type tumors</td>
<td>EGFR antibodies in combination with [chemotherapy] for patients with RASwt (BRAFwt) disease</td>
<td>EGFR antibodies in combination with [chemotherapy] for patients with RASwt (BRAFwt) disease</td>
</tr>
</tbody>
</table>

BRAF V600E: Lack of Benefit from EGFR inhibition

<table>
<thead>
<tr>
<th>Subgroup study</th>
<th>Sample size of Tx groups</th>
<th>PFS hazard ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmab/pmab</td>
<td>Comparator</td>
</tr>
<tr>
<td><strong>RAS WT / BRAF WT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRIME</td>
<td>228</td>
<td>218</td>
</tr>
<tr>
<td>CRYSTAL and OPUS</td>
<td>349</td>
<td>361</td>
</tr>
<tr>
<td>CO.17</td>
<td>101</td>
<td>97</td>
</tr>
<tr>
<td>20020408</td>
<td>63</td>
<td>52</td>
</tr>
<tr>
<td>PICCOLO</td>
<td>183</td>
<td>188</td>
</tr>
<tr>
<td>20050181</td>
<td>186</td>
<td>190</td>
</tr>
<tr>
<td>COIN</td>
<td>292</td>
<td>289</td>
</tr>
<tr>
<td><strong>Summary:</strong></td>
<td>1402</td>
<td>1415</td>
</tr>
</tbody>
</table>

Test for effect: $P < 0.001$
Heterogeneity: $I^2 = 82\%$, $P < 0.001$

<table>
<thead>
<tr>
<th><strong>RAS WT / BRAF WT</strong></th>
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<tr>
<td>PRIME</td>
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<td><strong>Summary:</strong></td>
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</table>

Test for effect: $P = 0.38$
Heterogeneity: $I^2 = 39\%$, $P = 0.13$

Roland, BJC '15
Acquired resistance to define EGFR sensitivity: Using tumor biology to evaluate innate resistance

“Selective Pressure”

“No Selective Pressure”

Adapted from Goldberg et al. ESMO Open 2018;3:e000353
Acquired resistance to define EGFR sensitivity

There is no evidence of activity of EGFR inhibitors alone in BRAF V600E CRC

Parseghian et al ASCO ‘19
## Guideline Recommendations: BRAF mutation (V600E)

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<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>No specific recommendation</td>
<td>The cytotoxic triplet FOLFOXIRI ...</td>
<td>The cytotoxic triplet FOLFOXIRI ... potentially also in fit patients with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>potentially also in fit patients with tumour BRAF mutations</td>
<td>tumour BRAF mutations</td>
</tr>
</tbody>
</table>
Aggressive Tumor = Aggressive Chemotherapy?
FOLFOXIRI+B in BRAF mut

BRAF mut HR=0.55 (0.24 to 1.23)  P=Not Significant

Cremolini et al Lancet Oncology ‘15
## Guideline Recommendations: BRAF mutation (V600E)

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<tbody>
<tr>
<td><strong>BRAF targeted therapy</strong></td>
<td>• Vemurafenib, irinotecan, cetuximab</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Dabrafenib, Trametinib, Panitumumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Encorafenib, Binimetinib, Cetuximab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Vemurafenib (PLX4032)

**Refractory Melanoma**

81% Response Rate

Flaherty et al. NEJM ’10

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**Refractory Colorectal**

5% Response Rate

Kopetz et al. JCO’15
Targeting BRAF: Adaptive Resistance

Homeostatic regulation is a critical and nearly universal feature of biological systems.

Growth pathways like MAPK have a number of such feedback networks established.

Inhibition of a single node in the pathway results in a rapid compensation in the signaling to restore homeostasis.
Targeting BRAF: Adaptive Resistance

Homeostatic regulation is a critical and nearly universal feature of biological systems.

Growth pathways like MAPK have a number of such feedback networks established.

Inhibition of a single node in the pathway results in a rapid compensation in the signaling to restore homeostasis.
## Combination Studies for BRAF mutated CRC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response rate*</th>
<th>PFS (months)</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single/doublet RAF/MEK</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>5%</td>
<td>2.1</td>
<td>Kopetz, JCO 2015</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>11%</td>
<td>NR</td>
<td>Falchook, Lancet 2008</td>
</tr>
<tr>
<td>Encorafenib</td>
<td>16%</td>
<td>NR</td>
<td>Gomez-Roca, ESMO 2014</td>
</tr>
<tr>
<td>Dabrafenib + trametinib</td>
<td>12%</td>
<td>3.5</td>
<td>Corcoran, JCO 2015</td>
</tr>
<tr>
<td><strong>Doublet with EGFR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib + panitumumab</td>
<td>13%</td>
<td>3.2</td>
<td>Yeager et al, CCR 2015</td>
</tr>
<tr>
<td>Vemurafenib + cetuximab</td>
<td>4%</td>
<td>3.7</td>
<td>Hyman et al, NEJM 2015</td>
</tr>
<tr>
<td>Encorafenib + cetuximab</td>
<td>19%</td>
<td>3.7</td>
<td>van Geel et al, Can Disc 2017</td>
</tr>
<tr>
<td>Dabrafenib + panitumumab</td>
<td>10%</td>
<td>3.4</td>
<td>Atreya, ASCO 2015</td>
</tr>
<tr>
<td><strong>Triplet with EGFR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib + cetuximab + irinotecan</td>
<td>16%</td>
<td>4.4</td>
<td>Kopetz et al, ASCO 2017</td>
</tr>
<tr>
<td>Dabrafenib + trametinib + panitumumab</td>
<td>32%</td>
<td>4.2</td>
<td>Corcoran, ESMO 2016</td>
</tr>
<tr>
<td>Encorafenib + cetuximab + alpelisib</td>
<td>18%</td>
<td>4.2</td>
<td>van Geel et al, Can Disc 2017</td>
</tr>
<tr>
<td>Encorafenib + binimetinib + cetuximab</td>
<td>48%</td>
<td>8.0</td>
<td>Van Cutsem et al, JCO 2019</td>
</tr>
</tbody>
</table>

*Studies differ on whether unconfirmed or confirmed responses are reported. NR, not reported; PFS, progression-free survival.
VIC Regimen: Vemurafenib + Irinotecan + Cetuximab

35% response rate

Appendiceal Cancer
Colorectal Cancer
* Prior cetuximab therapy
VIC Regimen vs Cetux/Irinotecan: 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

R

Cetuximab + Irinotecan + Vemurafenib

Optional cross-over

PFS
Primary endpoint: progression-free survival

Cetuximab + irinotecan

Vemurafenib + cetuximab + irinotecan

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

April 18 2017 data cut-off; median follow-up: 7.3 months.
CI, confidence interval; HR, hazard ratio.
Increased response rate with VIC but no increased overall survival

CI, confidence interval; HR, hazard ratio; VIC, vemurafenib + cetuximab + irinotecan.

<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib + Cetux + Irino (n=46)*</th>
<th>Cetuximab + Irinotecan (n=46)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>6 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>5 (11%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (24%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>5 (11%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (15%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15 (33%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (4%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (20%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>8/49 (16%)</td>
<td>3/50 (6%)</td>
</tr>
</tbody>
</table>

Spectrum of Resistance to BRAF + EGFR

- EGFR pathway activation
- RAS mutations
- MEK mutations
- EGFR, KRAS amplifications
- ARAF, PTEN, GNAS mutations

MAPK pathway reactivation
These acquired RAS models are still sensitive to high dose MAPK inhibition.
Dabrafenib + Panitumumab + Trametinib

N=91 patients, 21% RR, PFS 4.2 months

Atreya et al ESMO ’16; Corcoran et al Cancer Disc ‘18
Addressing BRAF/EGFR Resistance
Response rate and PFS of BRAFi/EGFRI may be augmented by MEKi

Phase 3: Encorafenib + Cetuximab ± Binimetinib

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

Patient population
- BRAF V600E mutant
- 1-2 prior regimens in metastatic setting

Arm A - Triplet Therapy
Binimetinib + Encorafenib + Cetuximab
n=205

Arm B - Doublet Therapy
Encorafenib + Cetuximab
n=205

Arm C - Control Arm
FOLFIRI + Cetuximab or irinotecan + Cetuximab
n=205
Triplet combination is tolerated and active: 48% Response Rate

*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 CRC study interim analysis: Tomorrow 9:00, Aud A

Statistically significant improvement in ORR vs control

Statistically significant improvement in OS vs control

Reduced the risk of death by 48% versus control
“BRAF Mutations”: V600E and Atypical / Non-V600E mutations

- BRAF V600E: 7%
- Atypical or Non-V600 BRAF mutation: 4%
- BRAF wild type: 89%
Atypical (Non-V600E) BRAF mutations

Prognosis is similar to BRAF wild-type

Recently identified as acquired alterations in post-EGFR inhibitor treated tumors
# Understanding Class II and Class III Non-V600E BRAF\textsuperscript{mut}

<table>
<thead>
<tr>
<th></th>
<th>BRAF V600E Class I</th>
<th>Class II BRAF</th>
<th>Class III BRAF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>BRAF monomer</td>
<td>BRAF dimers</td>
<td>BRAF/CRAF dimers</td>
</tr>
<tr>
<td><strong>RTK (EGFR) Dependency</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Kinase activity</strong></td>
<td>High</td>
<td>High/Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td><strong>EGFRi sensitivity</strong></td>
<td>No</td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
<tr>
<td><strong>Potential Strategy</strong></td>
<td>BRAF, MEK, EGFR</td>
<td>RAF dimer inhibitors</td>
<td>RTK, MAPK combinations</td>
</tr>
</tbody>
</table>

![Diagram showing the signaling pathways for Class I, II, and III BRAF mutants](image-url)

**References:**
Yao et al. Nature ‘17
Conclusions

- BRAF^{V600E} mutations have poor prognosis and novel therapeutic options
- BRAF should be part of the routine testing panel
- No evidence for activity of EGFR inhibition for BRAF^{V600E} tumors
- Combination strategies to target BRAF^{V600E} have been successful
  - Single arm data for dabrafenib, trametinib, panitumumab
  - PFS but no OS benefit from vemurafenib, irinotecan, cetuximab (VIC)
  - OS benefit from binimetinib, encorafenib, cetuximab (BEACON)
- Non-V600E mutations represent a mixture of signaling mechanisms, and further research is needed to define EGFR sensitivity and targeting strategies
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- Gani Manyam
- George Calin, MD
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- Kenna Shaw, PhD
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- Curt Harris, NKI
- Aaron Schetter, NKI
- Chloe Atreya, UCSF
- Ryan Corcoran, MD, PhD

Post-doctoral positions available
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