How can we predict the success in anti-EGFR therapy?

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Targeting the EGFR pathway in CRC

- EGFR expression 27–99%
- EGFR mutation 1-2%
- KRAS mutation 45–50%
- NRAS mutation 5-8%
- BRAF mutation 5-10%
- MAPK

**Inhibitors**

- Anti-EGFR MoAbs: Cetuximab, Panitumumab
- (RAS inh.)
- RAF inh.
- MEK inh.
- ERK inh.
Primary resistance to anti-EGFR therapy in colorectal cancer

- Responder (15%)
- KRAS/PIK3CA/PTEN (15%)
- KRAS amplification (1%)
- KRAS-NRAS (35-45%)
- BRAF/PIK3CA/PTEN (5-10%)
- MET amplification (2%)
- BRAF (5-10%)
- HER2 amplification (3%)
- PIK3CA and/or PTEN (15%)
- Non responder (16%)

Modified from Bardelli, J Clin Oncol 2010
RAS mutations induce continuous activation without retro-control

**Wild-type RAS**
- Inactive: RAS-GDP
- Active: RAS-GTP

**Mutant RAS**
- Inactive: RAS-GDP
- Active: RAS-GTP

**Normal:**
- Growth
- Proliferation
- Differentiation

**Abnormal:**
- Growth
- Proliferation
- Differentiation

Benefit from anti-EGFRs in the selected population early development late treatment lines

The magnitude of benefit from anti-EGFR moAbs is amplified in *KRAS* exon 2 wt population

<table>
<thead>
<tr>
<th></th>
<th>mPFS (mos)</th>
<th></th>
<th></th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Cet</td>
<td>BSC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unselected</td>
<td>572</td>
<td>1.9</td>
<td>1.8</td>
<td>0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>KRAS</em> exon 2 wt</td>
<td>215</td>
<td>3.7</td>
<td>1.9</td>
<td>0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>KRAS</em> exon 2 mut</td>
<td>151</td>
<td>1.8</td>
<td>1.8</td>
<td>0.99</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>mPFS (mos)</th>
<th></th>
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<th>HR</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Pan</td>
<td>BSC</td>
<td></td>
<td></td>
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<tr>
<td>Unselected</td>
<td>463</td>
<td>1.8</td>
<td>1.7</td>
<td>0.54</td>
<td>0.66</td>
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<tr>
<td><em>KRAS</em> exon 2 wt</td>
<td>243</td>
<td>2.8</td>
<td>1.7</td>
<td>0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>KRAS</em> exon 2 mut</td>
<td>184</td>
<td>1.7</td>
<td>1.7</td>
<td>0.99</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Jonker et al, N Engl J Med 2007*  
*Karapetis et al, N Engl J Med 2008*

*Van Cutsem et al, J Clin Oncol 2007*  
*Amado et al, J Clin Oncol 2008*
Overall patient population

Crystal study in mCRC no biomarker

CRYSTAL

Cetuximab + CT (FOLFIRI) (n=599)
CT (FOLFIRI) (n=599)

OS estimate

HR=0.878
p=0.0419

19.9 months
18.6 months

Crystal study in mCRC: KRAS (exon 2) status as a biomarker

Effect of EGFR inhibitor treatment in KRAS (exon 2) wt population: Consistency of data across trials

CRystal\textsuperscript{1} \hspace{1cm} OPUS\textsuperscript{2} \hspace{1cm} PRime\textsuperscript{3}

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cet + FOLFIRI</td>
<td>316</td>
<td>23.5 (21.2–26.3)</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>350</td>
<td>20.0 (17.4–21.7)</td>
</tr>
<tr>
<td>Cet + FOLFOX4</td>
<td>82</td>
<td>22.8 (19.3–25.9)</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>97</td>
<td>18.5 (16.4–22.6)</td>
</tr>
<tr>
<td>Pani + FOLFOX4</td>
<td>325</td>
<td>23.8 (20.0–27.7)</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>331</td>
<td>19.4 (17.4–22.6)</td>
</tr>
</tbody>
</table>

HR 0.80
(95\% CI 0.670–0.946)
p=0.0093
HR 0.86
(95\% CI 0.599–1.219)
p=0.39
HR 0.83
(95\% CI 0.70–0.98)
p=0.027

Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown\textsuperscript{4}

4. Erbitux SmPC June/2014
KRAS wt or mt status: until recently the only validated predictive biomarker for anti-EGFR antibodies in mCRC

- **KRAS wt**
  - Responders
  - Many KRAS wt tumors are responsive to EGFR mAbs
  - Some KRAS wt tumors are resistant to EGFR mAbs

- **KRAS mt**
  - Non-responders
  - Most KRAS mutant tumors are resistant to EGFR mAbs
Initially: *KRAS* testing identifies mutations in codons 12 and 13 of exon 2

**KRAS**
- **EXON 2**: codons 12 and 13, 30-35%~8%
- **EXON 3**: codon 61, 4%
- **EXON 4**: codon 117-146, 6-7%

**NRAS**
- **EXON 2**: codons 12 and 13, 3-5%
- **EXON 3**: codon 61, 4-6%
- **EXON 4**: codon 117-146, 0-1%

*KRAS/NRAS* mutations outside *KRAS* exon 2 are now tested before using cetuximab and panitumumab.

**RAS**
CRYSTAL: RAS wt selection extended the PFS benefit with cetuximab + FOLFIRI

KRAS exon 2 wt population

367/430 patients with KRAS exon 2 wt tumors evaluated for RAS status were RAS wt

Cetuximab should not be used for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown

3. Erbitux SmPC June/2014
CRYSTAL: RAS wt selection extended the ORR benefit with cetuximab + FOLFIRI

*KRAS evaluable in 430/666 (65%) patients with KRAS exon 2 wt mCRC; RAS wt: 367/430 (85%), 5% sensitivity cut-off; cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown.  

3. Erbitux SmPC June/2014
**Crystal study: Overall survival**

**KRAS codon 12/13 wild-type**

- **No. of events**: 242, 288
- **Median, months**: 23.5, 20.0
- **95% CI**: 21.2–26.3, 17.4–21.7
- **HR (95% CI)**: 0.80 (0.67–0.95)

**RAS wild-type**

- **No. of events**: 130, 154
- **Median, months**: 28.4, 20.2
- **95% CI**: 24.7–31.6, 17.0–24.5
- **HR (95% CI)**: 0.69 (0.54–0.88)


**Number of patients at risk**

- **KRAS codon 12/13 wild-type**
  - 316, 350
  - 281, 311
  - 237, 246
  - 198, 179
  - 144, 132
  - 108, 92
  - 82, 64
  - 65, 48
  - 21, 18
  - 4, 2

- **RAS wild-type**
  - 178, 189
  - 174, 182
  - 163, 171
  - 155, 160
  - 142, 135
  - 140, 115
  - 128, 98
  - 108, 85
  - 97, 79
  - 89, 70
  - 73, 58
  - 66, 47
  - 56, 38
  - 52, 32
  - 45, 28
  - 29, 20
  - 16, 10
  - 5, 6
  - 3, 2
  - 0, 0

**Presented by: Eric Van Cutsem**
## Crystal study: Efficacy: RAS subgroups

**PFS**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS codon 12/13 WT</td>
<td>666</td>
<td>0.70 (0.56–0.87)</td>
</tr>
<tr>
<td>KRAS codon 12/13 MT</td>
<td>397</td>
<td>1.17 (0.89–1.54)</td>
</tr>
<tr>
<td>RAS evaluable*</td>
<td>430</td>
<td>0.58 (0.44–0.77)</td>
</tr>
<tr>
<td>RAS WT</td>
<td>367</td>
<td>0.56 (0.41–0.76)</td>
</tr>
<tr>
<td>Any RAS MT†</td>
<td>460</td>
<td>1.10 (0.85–1.42)</td>
</tr>
<tr>
<td>Other RAS MT*</td>
<td>63</td>
<td>0.81 (0.39–1.67)</td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS codon 12/13 WT</td>
<td>666</td>
<td>0.80 (0.67–0.95)</td>
</tr>
<tr>
<td>KRAS codon 12/13 MT</td>
<td>397</td>
<td>1.04 (0.83–1.28)</td>
</tr>
<tr>
<td>RAS evaluable*</td>
<td>430</td>
<td>0.75 (0.60–0.93)</td>
</tr>
<tr>
<td>RAS WT</td>
<td>367</td>
<td>0.69 (0.54–0.88)</td>
</tr>
<tr>
<td>Any RAS MT†</td>
<td>460</td>
<td>1.05 (0.86–1.28)</td>
</tr>
<tr>
<td>Other RAS MT*</td>
<td>63</td>
<td>1.22 (0.69–2.16)</td>
</tr>
</tbody>
</table>

*KRAS codon 12/13 WT; †KRAS codon 12/13 or other RAS MT, mutant; WT, wild-type

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Presented by: Eric Van Cutsem

E Van Cutsem et al, J Clin Oncol 2015

ASCO 50th Annual Meeting
Science & Society

Favors FOLFIRI + cetuximab

Favors FOLFIRI

0.35 0.7 1.0 1.4 2.0

0.35 0.7 1.0 1.4 2.3
Expanded RAS mutation in PRIME

Panitumumab–FOLFOX4 Treatment and RAS Mutations in Colorectal Cancer

Jean-Yves Douillard, M.D., Ph.D., Kelly S. Oliner, Ph.D., Salvatore Siena, M.D., Josep Tabernero, M.D., Ronald Burkes, M.D., Mario Barugel, M.D., Yves Humblet, M.D., Ph.D., Gyorgy Bodoky, M.D., Ph.D., David Cunningham, M.D., Jacek Jassem, M.D., Ph.D., Fernando Rivera, M.D., Ph.D., Ilona Kocáková, M.D., Ph.D., Paul Ruff, M.D., Maria Błasińska-Morawiec, M.D., Martin Šmakal, M.D., Jean Luc Canon, M.D., Mark Rother, M.D., Richard Williams, M.B., B.S., Ph.D., Alan Rong, Ph.D., Jeffrey Wiezorek, M.D., Roger Sidhu, M.D., and Scott D. Patterson, Ph.D.

Refinement of patient population by WT RAS

**Progression-free survival**

**Original WT KRAS exon 2 testing**

<table>
<thead>
<tr>
<th></th>
<th>Events n (%)</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab + FOLFOX4 (n = 325)</td>
<td>199 (61)</td>
<td>9.6 (9.2–11.1)</td>
</tr>
<tr>
<td>FOLFOX4 (n = 331)</td>
<td>215 (65)</td>
<td>8.0 (7.5–9.3)</td>
</tr>
</tbody>
</table>

**WT RAS**

<table>
<thead>
<tr>
<th></th>
<th>Events n (%)</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab + FOLFOX4 (n = 259)</td>
<td>156 (60)</td>
<td>10.1 (9.3–12.0)</td>
</tr>
<tr>
<td>FOLFOX4 (n = 253)</td>
<td>170 (67)</td>
<td>7.9 (7.2–9.3)</td>
</tr>
</tbody>
</table>

HR = 0.80 (95% CI, 0.66–0.97)  
*P = 0.02

HR = 0.72 (95% CI, 0.58–0.90)  
*P = 0.004

*Predefined retrospective analysis; 7 patients harbouring Codon 59 mutations were not excluded from this analysis.

Excluding additional mutant tumors increases the relative proportion of responsive wt tumors

Increasing relative proportion of wt population responsive to EGFR mAbs

Detection of additional mutant tumors that are resistant to EGFR mAbs

Enhanced benefit profile for EGFR inhibitors in the more selected population
Are all *KRAS* mutations equal?

*KRAS* mutation frequency in patients with CRC: ~40%

<table>
<thead>
<tr>
<th>Amino acid substitution</th>
<th>Nucleic acid substitution</th>
<th>Relative Incidence %</th>
<th>Absolute Incidence %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Codon 12 mutations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate (G12D)</td>
<td>G35A</td>
<td>32.5</td>
<td>13</td>
</tr>
<tr>
<td>Valine (G12V)</td>
<td>G35T</td>
<td>22.5</td>
<td>9</td>
</tr>
<tr>
<td>Cysteine (G12C)</td>
<td>G34T</td>
<td>8.8</td>
<td>3</td>
</tr>
<tr>
<td>Serine (G12S)</td>
<td>G34A</td>
<td>7.6</td>
<td>3</td>
</tr>
<tr>
<td>Alanine (G12A)</td>
<td>G35C</td>
<td>6.4</td>
<td>3</td>
</tr>
<tr>
<td>Arginine (G12R)</td>
<td>G34C</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Codon 13 mutations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate (G13D)</td>
<td>G38A</td>
<td>19.5</td>
<td>8</td>
</tr>
<tr>
<td>Other mutations</td>
<td></td>
<td>1.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Differential effects of KRAS mutations in chemorefractory mCRC

- In patients receiving cetuximab monotherapy PFS and OS was longer for those with KRAS G13D mutated tumors vs other KRAS mutations.¹

- Patients with KRAS G13D mutant tumors have a worse prognosis under BSC.¹

<table>
<thead>
<tr>
<th>KRAS subset</th>
<th>OS median [95%CI]</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>wt</td>
<td>10.1 [9.4-11.3] vs. 5.0 [4.2-5.5]</td>
<td>0.60 [0.44-0.81]</td>
</tr>
<tr>
<td>G13D mt</td>
<td>7.6 [5.7-20.5] vs. 3.6 [2.2-4.8]</td>
<td>0.40 [0.13-1.28]</td>
</tr>
<tr>
<td>mt-other</td>
<td>5.7 [4.9-6.8] vs. 4.7 [3.6-6.7]</td>
<td>1.07 [0.74-1.60]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KRAS subset</th>
<th>PFS median [95%CI]</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>wt</td>
<td>4.2 [3.9-5.4] vs. 1.9 [1.8-2.0]</td>
<td>0.42 [0.32-0.56]</td>
</tr>
<tr>
<td>G13D mt</td>
<td>4.0 [1.9-6.2] vs. 1.7 [1.5-1.7]</td>
<td>0.53 [0.16-1.73]</td>
</tr>
<tr>
<td>mt-other</td>
<td>1.9 [1.8-2.8] vs. 1.8 [1.7-1.9]</td>
<td>0.93 [0.71-1.39]</td>
</tr>
</tbody>
</table>

BSC, best supportive care; CT, chemotherapy

¹De Roock W., Van Cutsem E, Tejpar S et al. JAMA 2010;304:1812-1820
**KRAS mutation status and treatment effect: PFS**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population (KRAS mutation)</th>
<th>Median (months) CT + cetuximab vs CT</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled analysis</td>
<td>wt (n=845)</td>
<td>9.6 vs 7.6</td>
<td>0.66 [0.55-0.80]</td>
</tr>
<tr>
<td></td>
<td>mt G13D (n=83)</td>
<td>7.4 vs 6.0</td>
<td>0.60 [0.32-1.12]</td>
</tr>
<tr>
<td></td>
<td>mt G12V (n=125)</td>
<td>5.6 vs 8.8</td>
<td>1.55 [0.94-2.56]</td>
</tr>
<tr>
<td></td>
<td>mt other (n=325)</td>
<td>6.7 vs 8.1</td>
<td>1.37 [1.02-1.84]</td>
</tr>
<tr>
<td>CRYSTAL</td>
<td>wt (n=666)</td>
<td>9.9 vs 8.4</td>
<td>0.69 [0.56-0.86]</td>
</tr>
<tr>
<td></td>
<td>mt G13D (n=60)</td>
<td>7.5 vs 7.4</td>
<td>0.72 [0.33-1.57]</td>
</tr>
<tr>
<td></td>
<td>mt G12V (n=91)</td>
<td>6.7 vs 8.2</td>
<td>1.43 [0.79-2.59]</td>
</tr>
<tr>
<td></td>
<td>mt other (n=246)</td>
<td>7.1 vs 7.7</td>
<td>1.19 [0.84-1.68]</td>
</tr>
<tr>
<td>OPUS</td>
<td>wt (n=179)</td>
<td>8.3 vs 7.2</td>
<td>0.57 [0.37-0.86]</td>
</tr>
<tr>
<td></td>
<td>mt G13D (n=23)</td>
<td>5.7 vs 5.6</td>
<td>0.40 [0.13-1.21]</td>
</tr>
<tr>
<td></td>
<td>mt G12V (n=34)</td>
<td>4.4 vs 9.4</td>
<td>1.89 [0.73-4.86]</td>
</tr>
<tr>
<td></td>
<td>mt other (n=79)</td>
<td>5.5 vs 8.6</td>
<td>2.06 [1.12-3.76]</td>
</tr>
</tbody>
</table>

CT, chemotherapy; mt, mutant; wt, wild-type

Tejpar S, ... Van Cutsem E, J Clin Oncol 2012
Mutant KRAS Codon 12 and 13 alleles in mCRC: Panitumumab studies

Fig 3. Pooled analysis of studies 20050203, 20050181, and 20020408: Predictive impact of mutant (MT) KRAS codon 12 and 13 alleles on (A) progression-free survival (PFS) and (B) overall survival (OS) in patients receiving either control (non-panitumumab-containing) or panitumumab-containing therapy. Point estimates for hazard ratios and their corresponding 95% CIs are plotted for the indicated mutant KRAS codon 12 and 13 alleles and are compared with the other mutant KRAS codon 12 and 13 alleles as a group.

Peeters M,…. Van Cutsem E et al, J Clin Onc 2012
ICECREAM Study schema

refractory mCRC (n=100) either quad WT (no mut in KRAS, BRAF, NRAF, PIK3CA ex 20) OR KRAS G13D mutation

RANDOMISATION 1:1
Stratified by:
Mutation status (quad WT vs G13D)
Institution

cetuximab
400mg/m² loading then 250mg/m² weekly

cetuximab + irinotecan
400mg/m² loading then 250mg/m² weekly
Irinotecan 180mg/m² q 14 days

Segelov E et al, ECC/ESMO 2015
ICECREAM:
G13D: 6 months Progression Free Survival

% event free at 6 m (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Event Free at 6m (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>10% (2-26%)</td>
</tr>
<tr>
<td>Cetux+ Irino</td>
<td>23% (9-40%)</td>
</tr>
</tbody>
</table>

Segelov E et al, ECC/ESMO 2015
ICECREAM
G13D: Maximal tumour response

Best response by RECIST

Cetuximab

Cetuximab + Irinotecan

Segelov E et al, ECC/ESMO 2015
Recommendation: RAS testing

- **RAS is a predictive biomarker for therapeutic choices** involving EGFR antibody therapies in the metastatic disease setting [1, A].
- **RAS testing is mandatory prior to treatment** with EGFR-targeted monoclonal antibodies cetuximab and panitumumab [1, A].
- Primary or metastatic colorectal tumour tissue can be used for RAS testing (see also **Recommendation 3**).
- **RAS analysis** should include at least KRAS exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and NRAS exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).
- **Turnaround time for RAS testing** (expanded RAS analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.
Recommendation: BRAF testing

- Tumour **BRAF mutation** status should be assessed alongside the assessment of tumour **RAS** mutational status for prognostic assessment and/or potential selection for clinical trials [1, B].
Treatment of metastatic disease

**CLINICAL CONDITION OF THE PATIENT**
- **Fit**
  - GOAL: Cytoreduction (Shrinkage)
  - MOLECULAR PROFILE:
    - **RAS wt**
      - Doublet + anti-EGFR
    - **RAS mt**
      - Combination + bevacizumab
    - **BRAF mt**
      - Triplet + bevacizumab
  - Re-evaluation/assessment of response every 2 months*
- **Unfit (but may be suitable)**
  - FP+-/ bevacizumab; reduced dose doublet; anti-EGFR

**GOAL**
- **Cytoreduction (Shrinkage)**
- **Disease control (Control progression)**

**MOLECULAR PROFILE**
- **RAS wt**
  - Doublet + anti-EGFR
  - CT + bevacizumab
  - CT + biological agent
- **RAS mt**
  - Combination + bevacizumab
  - CT + bevacizumab
- **BRAF mt**
  - Triplet + bevacizumab
  - Unusual, see text

**Re-evaluation/assessment of response every 2-3 months**

**GOAL**
- **Progressive disease**
  - Second-line
- **Disease control**
  - Continue; maintenance; or pause
- **Surgey**
  - Cytoreduction (Shrinkage)
  - Continue

**Unfit**
- **BSC**

*Re-evaluation/assessment of response every 2 months*

**Van Cutsem E, Cervantes A, Arnold D et al, ESMO consensus 2015 @ ESMO/WCGIC Barcelona 2015**
Anti-EGFR’s in later lines

- In RAS wild-type and BRAF wild-type patients not previously treated with EGFR antibodies cetuximab or panitumumab therapy should be considered
  - Cetuximab and panitumumab equally active as single agents
  - The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients
  - There is no unequivocal evidence to administer the alternate anti-EGFR antibody, if a patient is refractory to one of the anti-EGFR antibodies.

Van Cutsem E, Cervantes A, Arnold D et al, ESMO consensus 2015 @ ESMO/WCGIC Barcelona 2015
Pietrantonio meta-analysis: OS (BRAF mt)\(^1\)

- No significant benefit in OS demonstrated with anti-EGFR therapy vs standard care in patients with (K)RAS wt/BRAF mt

### Trial (n) | Weight, % | OS HR (95% CI)
--- | --- | ---
OPUS/CRYSTAL | 20.7 | 0.62 (0.36–1.06)
PRIME | 17.0 | 0.90 (0.46–1.76)
CO.17 | 6.0 | 0.84 (0.20–3.56)
PICCOLO | 21.5 | 1.84 (1.10–3.08)
20050181 | 16.4 | 0.64 (0.32–1.28)
FIRE-3 | 18.5 | 0.87 (0.47–1.61)
Summary | 100.0 | 0.91 (0.62–1.34)

Heterogeneity: \(\tau^2=0.11; \chi^2=10.09; \text{df}=5 \ (p=0.07); I^2=50\%\)

Test for overall effect: \(Z=0.48 \ (p=0.63)\)

Rowland et al meta-analysis: Treatment interaction for OS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Trial (n)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS wt/ BRAF wt</td>
<td>PRIME (n=446)</td>
<td>0.74 (0.57–0.96)</td>
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<tr>
<td></td>
<td>OPUS/CRYSTAL (n=730)</td>
<td>0.84 (0.71–1.00)</td>
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<tr>
<td></td>
<td>CO.17 (n=198)</td>
<td>0.52 (0.37–0.71)</td>
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<td>PICCOLO (n=371)</td>
<td>0.91 (0.74–1.13)</td>
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<td></td>
<td>20050181 (n=376)</td>
<td>0.83 (0.64–1.07)</td>
</tr>
<tr>
<td></td>
<td>COIN (n=627)</td>
<td>0.01 (0.84–1.22)</td>
</tr>
<tr>
<td></td>
<td>Summary (n=2748)</td>
<td>0.81 (0.70–0.95)</td>
</tr>
<tr>
<td>RAS wt./BRAF mt</td>
<td>PRIME (n=53)</td>
<td>0.90 (0.46–1.76)</td>
</tr>
<tr>
<td></td>
<td>OPUS/CRYSTAL (n=70)</td>
<td>0.62 (0.36–1.06)</td>
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<tr>
<td></td>
<td>CO.17 (n=10)</td>
<td>0.84 (0.20–3.58)</td>
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<tr>
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<td>PICCOLO (n=68)</td>
<td>1.84 (1.10–3.08)</td>
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<td>20050181 (n=45)</td>
<td>0.64 (0.32–1.28)</td>
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<tr>
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<td>COIN (n=102)</td>
<td>1.18 (0.76–1.81)</td>
</tr>
<tr>
<td></td>
<td>Summary (n=351)</td>
<td>0.97 (0.67–1.41)</td>
</tr>
</tbody>
</table>

No significant treatment × BRAF status interaction for OS (p=0.43)

Clinical and molecular correlates

**Canonical**
- High chromosomal instability
- Microsatellite stable
- CIMP negative
- WNT and MYC activation

**MSI - Immune**
- Microsatellite instability
- CIMP high
- Hypermutation, *BRAF* mutations
- Immune activation

**Metabolic**
- Heterogeneous chromosomal/microsatellite status
- *KRAS* mutations
- Metabolic reprogramming

**Mesenchymal**
- High chromosomal instability
- TGFβ activation
- Invasion, matrix remodeling
- Angiogenesis

**Immune checkpoint inhibitors**
- Immune regulators
- *BRAF* strategies

**TGFβ inhibitors**
- New antiangiogenics
- Matrix inhibitors

Dienstmann R. J Clin Oncol 2014
The consensus molecular subtypes of colorectal cancer

CMS1
MSI Immune
- MSI, CIMP high
- Hypermutation
- Immune infiltration and activation

CMS2
Canonical
- SCN high
- WNT and MYC activation

CMS3
Metabolic
- Mixed MSI status
- SCNA low, CIMP low
- Metabolic deregulation

CMS4
Mesenchymal
- SCN high
- Stromal infiltration
- TGF beta activation
- Angiogenesis

CIMP, CpG island methylator phenotype; MSI, microsatellite instability; TGF, transforming growth factor

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