What to do after failure of first line treatment of metastatic CRC?

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Disclosures

- participation to advisory boards for Array, Astrazeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi, GSK, Pierre-Fabre, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier, Sirtex, Taiho
- research grants from Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Roche, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier paid to institution
A classical case of mCRC in 2019
CONTINUUM OF CARE

1991: OS 6 months

Locoregional therapy: toolbox: surgery, HIPEC, RFA, Radioembolisation,…

5 months first-line induction
6 months maintenance
3 months reintroduction (or treatment beyond progression)

3 months break
4 months second line
3 months third line
3 months “rechallenge” or fourth line
3 months preterminal phase

OS 30 months
The continuum of care of mCRC

Fluoropyrimidines: 5FU, capecitabine, S1, Triflurdine/tipiracil
Oxaliplatin
Irinotecan

Surgery (RFA)

1st line cytotoxic → 2nd line cytotoxic → 3rd line cytotoxic

Maintenance strategy

At progression change chemo, biologic or both?

Independent sequences?

1st line biologic

Bevacizumab/aflibercept/ramucirumab
Cetuximab/panitumumab
Regorafenib

2nd line biologic

Pembrolizumab/nivolumab ± ipilimumab
Encorafenib + binimetinib; vemurafenib
Trastuzumab + lapatinib or pertuzumab
Larotrectinib

3rd line biologic

Locoregional therapy: SIRS

How to start?
What is best strategy?
How to select?
What to do for liver (lung/peritoneal) metastases?
Table 4: Drivers for first-line treatment

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>Patient characteristics</th>
<th>Treatment characteristics</th>
</tr>
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<tbody>
<tr>
<td>Clinical presentation:</td>
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<td>Tumour burden</td>
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<td>Tumour localisation</td>
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<td>Performance status</td>
<td>Flexibility of treatment administration</td>
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<td>Comorbidities, patient attitude, expectation and preference</td>
<td>Quality of life</td>
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Ann Oncol, July 2016
<table>
<thead>
<tr>
<th>Line of systemic treatment</th>
<th>Realistic treatment goal</th>
</tr>
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<tbody>
<tr>
<td>Adjuvant</td>
<td>&quot;Cure&quot;</td>
</tr>
<tr>
<td></td>
<td>Reduce risk of recurrence</td>
</tr>
<tr>
<td></td>
<td>Maximal tumor response</td>
</tr>
<tr>
<td></td>
<td>Enabling local ablation and/or long duration of low/no tumor burden</td>
</tr>
<tr>
<td>1st line</td>
<td>Durable disease control</td>
</tr>
<tr>
<td></td>
<td>Tumor response if needed</td>
</tr>
<tr>
<td>2nd line</td>
<td>Durable disease control</td>
</tr>
<tr>
<td></td>
<td>Maintenance of QOL and PS</td>
</tr>
<tr>
<td>3rd line</td>
<td>Disease control</td>
</tr>
<tr>
<td></td>
<td>and maintenance of QOL; palliation</td>
</tr>
<tr>
<td>Subsequent lines</td>
<td></td>
</tr>
</tbody>
</table>
TRIBE-2 Sequencing trial

Arm A
FOLFOX + bev* 5FU/bev → PD1 → FOLFIRI + bev* 5FU/bev → PD2

Arm B
FOLFOXIRI + bev* 5FU/bev → PD1 → FOLFOXIRI + bev* 5FU/bev → PD2

Progression Free Survival 2 (primary EP)

* Up to 8 cycles

Cremolini C et al., ESMO GI/WCGIC 2019
TRIBE-2 Sequencing trial:
PFS 2: Primary Endpoint

Median follow up = 30.6 mos

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>N =</td>
<td>340</td>
<td>339</td>
</tr>
<tr>
<td>Events, N (%)</td>
<td>272 (80%)</td>
<td>242 (71%)</td>
</tr>
<tr>
<td>Median PFS2, mos</td>
<td>17.5</td>
<td>19.1</td>
</tr>
</tbody>
</table>

HR = 0.74 [95% CI: 0.62-0.88]  
p<0.001

Cremolini C et al., ESMO GI/WCGIC 2019
**TRIBE-2 Sequencing trial: Secondary Endpoints**

### 1st-line ORR

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX + bev N = 340</th>
<th>FOLFOXIRI + bev N = 339</th>
<th>OR [95%CI], p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Partial Response</td>
<td>46%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td><strong>Response Rate</strong></td>
<td>50%</td>
<td>62%</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>40%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>7%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Not Assessed</td>
<td>3%</td>
<td>5%</td>
<td>p=0.047</td>
</tr>
<tr>
<td>R0 Resection Rate</td>
<td>12%</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

### 1st-line PFS

<table>
<thead>
<tr>
<th></th>
<th>Median follow up = 30.6 mos</th>
<th>FOLFOX + bev N = 340</th>
<th>FOLFOXIRI + bev N = 339</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, N (%)</td>
<td>303 (89%)</td>
<td>291 (86%)</td>
<td></td>
</tr>
<tr>
<td>Median 1st PFS, mos</td>
<td>9.8</td>
<td>12.0</td>
<td>HR = 0.75 [95% CI: 0.63-0.88] p=0.001</td>
</tr>
</tbody>
</table>

### OS – preliminary results

<table>
<thead>
<tr>
<th></th>
<th>Median follow up = 30.6 mos</th>
<th>Arm A N = 340</th>
<th>Arm B N = 339</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, N (%)</td>
<td>217 (64%)</td>
<td>191 (56%)</td>
<td></td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>22.6</td>
<td>27.6</td>
<td>HR = 0.81 [95% CI: 0.67-0.98] p=0.033</td>
</tr>
</tbody>
</table>

Cremolini C et al., ESMO GI/WCGIC 2019
**Clinical Update in thinking based on data:**
* molecular analysis esp. for druggable markers: MSI, BRAF, HER2, NTRAK fusions, POLE mutation: **targeted agents or IO agents**

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**Table 7. Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment goal</th>
<th>Cytoreduction (tumour shrinkage)</th>
<th>Disease control (control of progression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular profile</td>
<td>RAS wt</td>
<td>CT doublet + bevacizumab</td>
<td>CT doublet + EGFR antibody or FOLFIRI + aflibercept/ramucirumab</td>
</tr>
<tr>
<td>Second line</td>
<td>RAS mt</td>
<td>CT doublet + bevacizumab</td>
<td>FOLFIRI + aflibercept/ramucirumab</td>
</tr>
<tr>
<td>Preferred choice(s)</td>
<td>BRAF mt</td>
<td>CT doublet + bevacizumab</td>
<td>FOLFIRI + aflibercept/ramucirumab</td>
</tr>
<tr>
<td>Second choice</td>
<td>RAS wt</td>
<td>CT doublet + bevacizumab</td>
<td>FOLFIRI + aflibercept/ramucirumab</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td>CT doublet + bevacizumab</td>
<td>FOLFIRI + aflibercept/ramucirumab</td>
</tr>
</tbody>
</table>

Online Ann Oncol, July 2016
## Cross trial comparison (caution...!) with 2L strategies

<table>
<thead>
<tr>
<th></th>
<th>EPIC(^1)</th>
<th>Study 181(^2)</th>
<th>VELOUR(^3)</th>
<th>E3200(^4)</th>
<th>TML(^5)</th>
<th>RAISE(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cetux + Iri</strong> (n=97)</td>
<td>10.9</td>
<td>11.6</td>
<td>14.5</td>
<td>12.5</td>
<td>13.5</td>
<td>12.9</td>
</tr>
<tr>
<td><strong>Iri</strong> (n=95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Panit + FOLFIRI</strong> (n=303)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FOLFIRI</strong> (n=294)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aflib + FOLFIRI</strong> (n=612)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plac + FOLFIRI</strong> (n=614)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bev + FOLFOX4</strong> (n=286)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FOLFOX</strong> (n=291)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bev + CT</strong> (n=410)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CT</strong> (n=409)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RAM + FOLFIRI</strong> (n=536)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plac + FOLFIRI</strong> (n=536)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mOS, months</strong></td>
<td>10.9</td>
<td>11.6</td>
<td>14.5</td>
<td>12.5</td>
<td>13.5</td>
<td>12.9</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>1.28</td>
<td>0.85</td>
<td>0.82</td>
<td>0.75</td>
<td>0.81</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>NR</td>
<td>0.12</td>
<td>0.0032</td>
<td>0.0011</td>
<td>0.0062</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>mPFS, months</strong></td>
<td>4.0</td>
<td>2.8</td>
<td>5.9</td>
<td>3.9</td>
<td>6.9</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.77</td>
<td>0.73</td>
<td>0.76</td>
<td>0.61</td>
<td>0.68</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>NR</td>
<td>&lt;0.004</td>
<td>0.00007</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>10.3</td>
<td>7.4</td>
<td>35</td>
<td>10</td>
<td>19.8</td>
<td>11.1</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>NR</td>
<td>&lt;0.001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.3113</td>
<td>0.6336</td>
</tr>
</tbody>
</table>

6. Tabernero ...Van Cutsem et al, Lancet Oncol 2015
Post-progression:
Chemotherapy ± bevacizumab: ML18147

Median PFS: 5.7 mo vs 4.1 mo

Bennouna J…Van Cutsem E et al. Lancet Oncol 2013
VELOUR STUDY: results

Van Cutsem E et al., J Clin Oncol 2012
Figure 2: Kaplan-Meier survival estimates in the intention-to-treat population
(A) Overall survival and (B) progression-free survival in patients receiving ramucirumab and FOLFIRI compared with that in patients receiving placebo and FOLFIRI, stratified by geographical region, KRAS exon 2 status, and time to disease progression after the start of first-line therapy. FOLFIRI-leucovorin, fluorouracil, and irinotecan.

## Differences in toxicity??

<table>
<thead>
<tr>
<th></th>
<th>TML1</th>
<th>VELOUR²</th>
<th>RAISE³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT</td>
<td>CT + BEV</td>
<td>FOLFIRI</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>?</td>
<td>?</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Mucosal inf.</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Infection</td>
<td>?</td>
<td>?</td>
<td>7</td>
</tr>
<tr>
<td>VTE</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>GI perforation</td>
<td>&lt;1</td>
<td>2</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

3. Tabernero ...Van Cutsem et al, Lancet Oncol 2015
Recommendation 20: Second-line combinations with targeted agents

- Patients who are bevacizumab naïve should be considered for treatment with an antiangiogenic (bevacizumab or aflibercept) second-line [I, A]. The use of aflibercept should be restricted to combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen [I, A].

- Patients who received bevacizumab first-line should be considered for treatment with:
  - Bevacizumab post-continuation strategy [I, A]
  - Aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin [I, A]
  - EGFR antibodies in combination with FOLFIRI/irinotecan for patients with RAS wild-type (BRAF wild-type) disease
    - Relative benefit of EGFR antibodies is similar in later lines compared with second-line [II, A].

- Patients who are fast progressors on first-line bevacizumab-containing regimens, should be considered for treatment with aflibercept or ramucirumab (only in combination with FOLFIRI) [II, B], and - in the case of patients with RAS wild-type disease and no pre-treatment with anti-EGFR therapy - EGFR antibody therapy, preferably in combination with chemotherapy [II, B].
High VEGF-A and PlGF serum levels may underlie development of resistance to bevacizumab in patients with mCRC. Aflibercept retains its activity regardless of baseline VEGF-A and PlGF levels and may be an effective second-line treatment for patients with bevacizumab-induced resistance.
Table 4: Drivers for first-line treatment
many are also valid in later line

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<tr>
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<td>Comorbidities, patient attitude, expectation and preference</td>
<td>Quality of life</td>
</tr>
</tbody>
</table>

Patient and treatment characteristics become even more relevant in later lines

Ann Oncol, July 2016
ESMO consensus guideline:
Third-line choice

Clinical Update in thinking based on data:
* molecular analysis esp. for druggable markers: MSI, BRAF, HER2, NTRAK fusions, POLE mutation: targeted agents or IO agents

Ann Oncol, July 2016
Regorafenib inhibits VEGFR1, VEGFR2, VEGFR3 AND other Pathways, including RET, KIT, PDGFRα, PDGFRβ, FGFR1, FGFR2, TIE2, BRAF, BRAFv600E.


FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; TIE2, tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2; VEGF, vascular endothelial growth factor.
**Trifluridine/tipiracil**

**mechanism of action**

**F3dThd (FTD)**
- Thymidine-based nucleoside analogue
- Inhibition of tumor growth
- DNA dysfunction

**TAS-102**
- Molar ratio = 1 : 0.5
- FTD : Trifluridine
- TPI : Tipiracil-HCl

**FTD incorporation into DNA**
Trifluridine/tipiracil ≠ 5-FU rechallenge

dTMP, deoxythymine diphosphate; dUMP, deoxyuridine diphosphate; dUTP, deoxyuridine triphosphate; FdUDP, fluorodeoxyuridine diphosphate; FdUMP, fluorodeoxyuridine monophosphate; FdUTP, fluorodeoxyuridine triphosphate; 5-FU, 5-fluorouridine; FUDP, fluorouridine diphosphate; FUMP, fluorouridine monophosphate; FUTP, fluorouridinetriphosphate; FUR, fluorouridine; MoA, mechanism of action; TS, thymidylate synthase; UFT, tegafur-uracil.

Regorafenib phase III studies

**CORRECT**¹

Patients with mCRC who had progressed after standard therapy (N = 760)¹

Regorafenib + BSC

Placebo + BSC

2:1

**CONCUR**²

Asian patients with mCRC who had progressed after standard therapy (N = 204)²

Regorafenib + BSC

Placebo + BSC

2:1

**CONSIGN**³

Patients with mCRC who had progressed after standard therapy (N = 2872)³

Regorafenib

Primary endpoint

<table>
<thead>
<tr>
<th>Regorafenib (n = 505)</th>
<th>Placebo (n = 255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4</td>
<td>5.0</td>
</tr>
<tr>
<td>HR = 0.77; 95% CI (0.64–0.94)</td>
<td></td>
</tr>
<tr>
<td>P = .052</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regorafenib (n = 136)</th>
<th>Placebo (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.8</td>
<td>6.3</td>
</tr>
<tr>
<td>HR = 0.55; 95% CI (0.40–0.77)</td>
<td></td>
</tr>
<tr>
<td>P = .00016</td>
<td></td>
</tr>
</tbody>
</table>

Trifluridine/tipiracil randomised Phase II/III clinical development program

JAPICCTI-090880¹
Phase 2 N=169)
mCRC patients refractory to ≥2 prior regimens
ECOG PS score 0–2
Adequate bone marrow and organ function

RE COURSE²
Phase 3 (N=800)
mCRC patients refractory to ≥2 prior regimens
ECOG PS score ≤1
Adequate bone marrow and organ function
Known KRAS status

TERRA³
Phase 3 (N=406)
East Asian mCRC patients refractory to ≥2 prior regimens
ECOG PS score ≤1

PRECONNECT⁴
Phase 3 (N=300)
Ongoing, planned for 1000 pts.
mCRC patients
ECOG-Performance Status (PS) <2 and were refractory/intolerant to available therapies⁴

- Trifluridine/tipiracil BID PO + BSC (N=112)
- Placebo + BSC (N=57)
- Trifluridine/tipiracil BID PO + BSC (N=534)
- Placebo + BSC (N=266)
- Trifluridine/tipiracil BID PO + BSC (N=271)
- Placebo + BSC (N=135)
- Trifluridine/tipiracil BID PO + BSC (N=300)

*East Asian specific study
Trifluridine/tipiracil prescribing information is available at this meeting
BID, twice daily; BSC, best supportive care; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival;
PO, orally; q4w, every 4 weeks; RR, response rate; TTF, time to treatment failure
Regorafenib and trifluridine/tipiracil in refractory mCRC:

CORRECT: regorafenib

RE COURSE: trifluridine/tipiracil

Optimal Sequence in chemorefractory patients?

Regorafenib → Trifluridine/tipiracil

or

Trifluridine/tipiracil → Regorafenib

Considerations:
- Different safety pattern
  - Trifluridine/tipiracil: more favourable safety patterns, but what if compared to lower starting dose of regorafenib
  - No predictive markers for benefit, nor clearly differential patient characteristics
Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study

ReDOS study

Figure 2: Overall survival (A) and progression-free survival (B) in the dose-escalation and standard-dose groups.

Censored patients are marked on the curves with a cross.
QOL in ReDOS study

Bekaii-Saab T et al; The Lancet Oncology 2019: DOI: (10.1016/S1470-2045(19)30272-4)
N: 299 patients

Primary endpoint:
- **Safety**: % of patients having G3/G4 AEs during the entire course of the treatment

Secondary endpoints:
- OS
- PFS
- % of Patients starting C3 on each arm
- Dose intensity
- DCR

Argiles G et al, ESMO GI/WCGIC 2019
Primary Endpoint: Pts having G3/G4 AEs during treatment course

Arm A: 60%  
Arm B: 54%  
Arm C: 55%  

Threshold to reach positivity in the 2 experimental arms

Argiles G et al, ESMO GI/WCGIC 2019
Future: combination studies

Appealing combinations:

- Interesting phase 2 study: trifluridine/tipiracil + bevacizumab

- Very interesting study, but preliminary data in Asian patients: regorafenib + nivolumab

Pfeiffer P et al, ESMO GI/WCGIC 2019; Hara H et al, ESMO GI/WCGIC 2019
Conclusions:
These findings support the introduction of an approved agent such as trifluridine/tipiracil or regorafenib beyond the second line before any rechallenge in patients with mCRC who have failed second-line treatment.
ESMO consensus guideline:
Third-line choice

Clinical Update in thinking based on data:
* molecular analysis esp. for druggable markers: MSI, BRAF, HER2, NTRAK fusions, POLE mutation: targeted agents or IO agents

Ann Oncol, July 2016
Genomic markers

- RAS mut +/- PIK3CA/PTEN mut: 45%
- PIK3CA/PTEN mut: 8%
- Wild-type anti-EGFR therapies: 26%
- BRAF V600E
- BRAF inh + anti-EGFR +/- MEK inh
- MSI
- MSI + other
- POLE mut
- HER2 ampl
- MET ampl
- MET inh
- Gene fusion
- Kinase inh
- double anti-HER2
- anti-PD1/L1

Dienstmann et al, ASCO Ed Book 2018
MSI predictive value in mCRC
Studies in pretreated patients

Prevalence ~ 5%

PEMBROLIZUMAB

NIVOLUMAB

NIVOLUMAB + IPILIMUMAB

Le et al. Science 2017

Overman... Van Cutsem et al. J Clin Oncol 2018; Overman et al. Lancet Oncol 2017
Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164

FIG 1. Best percentage change from baseline in target lesion size (RECIST v1.1, central review) by prior line in patients with MSI-H/dMMR colorectal cancer in (A) Cohort A and (B) Cohort B

<table>
<thead>
<tr>
<th>Best response</th>
<th>Cohort A N = 61</th>
<th>Cohort B N = 63</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) 95% CI</td>
<td>n (%) 95% CI</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>20 (33) 21-46</td>
<td>21 (33) 22-46</td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (3) 0-11</td>
<td>5 (8) 3-18</td>
</tr>
<tr>
<td>Partial response</td>
<td>18 (30) 19-43</td>
<td>16 (25) 15-38</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11 (18) 9-30</td>
<td>15 (24) 14-36</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>28 (46) 33-59</td>
<td>25 (40) 28-53</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>2 (3) 0-11</td>
<td>2 (3) 0-11</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>31 (51) 38-64</td>
<td>36 (57) 44-70</td>
</tr>
<tr>
<td>Median time to response, months (range)</td>
<td>4 (2-25)</td>
<td>4 (2-13)</td>
</tr>
<tr>
<td>Median duration of response, months (range)</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

TABLE 2. Best Response (RECIST v1.1, central review) in Patients with MSI-H/dMMR Colorectal Cancer

Le E, Kim T, Van Cutsem E et al, J Clin Oncol, online Nov 14, 2019
### Table 2: Objective response, best overall response, and disease control per investigator and masked independent central review assessments

<table>
<thead>
<tr>
<th>Objective response</th>
<th>Investigator</th>
<th>Blinded independent central review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>23 (31.1%, 20.8-42.9)</td>
<td>24 (32%, 22.4-44)</td>
</tr>
<tr>
<td>Best overall response</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>23 (31%)</td>
<td>22 (30%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>28 (38%)</td>
<td>25 (34%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>19 (26%)</td>
<td>21 (28%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4 (5%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Not determined</td>
<td>51 (69%, 57-79)</td>
<td>47 (64%, 52-74)</td>
</tr>
</tbody>
</table>

Data are n (%). dMMR/MSI-H: DNA mismatch repair deficient/microsatellite instability-high.
Durable Responses with nivolumab + ipilimumab in MSI-H pretreated mCRC

Table 2. ORR, Best Overall Response, and DCR per Investigator Assessment (N = 119)

<table>
<thead>
<tr>
<th>Response</th>
<th>No. (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>65 (55)</td>
<td>45.2 to 63.8</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>61 (51)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>37 (31)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>14 (12)</td>
<td></td>
</tr>
<tr>
<td>Not determined</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Disease control for ≥ 12 weeks</td>
<td>95 (80)</td>
<td>71.5 to 86.6</td>
</tr>
</tbody>
</table>

Abbreviations: DCR, disease control rate; ORR, objective response rate.

A

Best Reduction From Baseline in Target Lesion Size (%)

Overman M….Van Cutsem E et al, J Clin Onc 2018
Conclusions:
check-point inhibitors in mCRC

- Pembrolizumab provided durable responses in MSI-H CRC patients who received ≥1 prior therapy
- Nivolumab with or without ipilimumab provided durable responses in MSI-H CRC patients who received ≥1 prior therapy
- Nivolumab plus ipilimumab active in first line treatment of MSI-H CRC patients
- Nivolumab and pembrolizumab (chemorefractory) and atezolizumab (maintenance): no activity in MSS patients
- Nivolumab + ipilimumab: no activity (very modest) in MSS patients
- Atezolizumab + cobimetinib no activity in pretreated MSS patients
- Darvalumab + tremelimumab: modest survival benefit, but no PFS improvement in randomized phase 2 compared to BSC in MSS patients - TBC

- Ongoing phase 3 studies in earlier lines in MSI tumors: e.g.
  - Stage III: FOLFOX ± CPI
  - First line compared to chemo in MSI (KEYNOTE-177 study (NCT02563002))
Triple MAPK Pathway Inhibition in BRAF-mutant CRC

- **BRAF**\(^{V600}\) mutation occurs in 10%–15% of patients and confers a poor prognosis\(^1-3\)
- BRAF inhibitors alone are ineffective due to the feedback activation of EGFR, leading to continued cell proliferation\(^4-6\)
  - Feedback may be overcome by targeting multiple pathway nodes, ie BRAF/MEK/EGFR
  - Preclinically, addition of MEK inhibitor improved outcomes
- In the BEACON CRC safety-lead in study, the triplet regimen of Encorafenib (ENCO) + Binimetinib (BINI) + Cetuximab (CETUX) had manageable safety profile and encouraging activity in patients with **BRAF**\(^{V600E}\) mCRC\(^7\)

**MAPK Signaling in Colorectal Cancer**\(^8\)

**HT-29 BRAF**\(^{V600E}\) Colorectal Xenografts\(^9\)

---

**CETUX**=cetuximab; **EGFR**=epidermal growth factor receptor; **ENCO**=encorafenib; **MAPK**=mitogen-activated protein kinase; **mCRC**=metastatic colorectal cancer; **PFS**=progression-free survival; **ORR**=objective response rate; **OS**=overall survival.


**BRAF**<sub>V600E</sub> mutation in mCRC

- Occurs in 8%-15% of patients and confers a poor prognosis
- Standard therapies have limited benefits after ≥1 line of treatment
- BRAF inhibitors cause feedback activation of EGFR in BRAF-mutant CRC, leading to continued cell proliferation

### Targeting BRAF\textsuperscript{V600E}: studies to date

<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, J Clin Oncol 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, J Clin Oncol 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., Clin Cancer Res 2015</td>
</tr>
<tr>
<td>vemurafenib + cetuximab</td>
<td>4%</td>
<td>3.7</td>
<td>Hyman et al., New Engl J Med 2015</td>
</tr>
<tr>
<td>encorafenib + cetuximab</td>
<td>19%</td>
<td>3.7</td>
<td>van Geel et al., Cancer Discov 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, Van Cutsem et al, Cancer Discovery 2018</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., J Clin Onc 2019</td>
</tr>
</tbody>
</table>
Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E–Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study

Eric Van Cutsem, MD, PhD; Sanne Huijberts, MD; Axel Grothey, MD; Rona Yaeger, MD; Pieter-Jan Cuyler, MD; Elena Elez, MD, PhD; Marwan Fakih, MD; Clara Montagut, MD; Marc Peeters, MD, PhD; Takayuki Yoshino, MD; Harpreet Wasan, MD; Jayesh Desai, MBBS; Fortunato Ciardiello, MD, PhD; Ashwin Gollerkeri, MD; Janna Christy-Bittel, MSN; Kati Maharry, PhD; Victor Sandor, MD; Jan H.M. Schellens, MD, PhD; Scott Kopetz, MD, PhD; and Josep Taberner, MD, PhD

BEACON Study: lead in part

Triple combination: EGFR inhibitor (cetuximab) + BRAF inhibitor (encorafenib) + MEK inhibitor (binimetinib)

Best % Change from Baseline

Confirmed RR: 48%  
PFS: 8.0 mo  
Med Surv: 15.3 mo

*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.

Van Cutsem E et al, J Clin Oncol 2019
Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer

Phase III: BEACON Study

Results of Safety Lead-In led to the introduction of an additional primary endpoint of ORR and an interim OS analysis to allow for early assessment.

Patients with \(BRAF^{V600E}\) mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor.

---

**Safety Lead-in**

**Triplet therapy**

ENCO + BINI + CETUX

\(n = 30\)

Encorafenib 300 mg PO daily
Binimetinib 45 mg PO bid
Cetuximab standard weekly dosing

A separate Safety Lead-in cohort of \(n=7\) in Japan was enrolled subsequently. Results will be reported at a later time.

**Phase 3**

**R**

1:1:1

**Triplet therapy**

ENCO + BINI + CETUX

\(n = 205\)

**Control arm**

FOLFIRI + CETUX, or irinotecan + CETUX

\(n = 205\)

---

**Secondary Endpoints:** Doublet vs Control OS & ORR, PFS, Safety

**Primary Endpoints:**

- OS
- ORR (Blinded Central Review)

Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved).

Phase III: BEACON Study

Primary Endpoint - Overall Survival: Triplet vs Control (all randomized patients)

Median OS in months (95% CI)

**Triplet**  
9.0 (8.0–11.4)

**Control**  
5.4 (4.8–6.6)

HR (95% CI), 0.52 (0.39–0.70)  
2-sided $P<0.0001$
Overall Survival and Objective Response Rate

**Triplet vs Control**

HR (95% CI): 0.52 (0.39-0.70)
2-sided P<0.0001

**Control**

Median OS in months (95% CI)
Triplet 9.0 (8.0-11.4)
Control 5.4 (4.8-6.6)

**Doublet vs Control**

HR (95% CI): 0.60 (0.45-0.79)
2-sided P=0.0003

**Control**

Median OS in months (95% CI)
Doublet 8.4 (7.5-11.0)
Control 5.4 (4.8-6.6)

**Objective Response Rate (First 331 Randomized Patients)**

<table>
<thead>
<tr>
<th>Confirmed Response by BICR</th>
<th>Triplet N=111</th>
<th>Doublet N=113</th>
<th>Control N=107</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response Rate</strong></td>
<td>26%</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>95% (CI)</td>
<td>(18, 35)</td>
<td>(13, 29)</td>
<td>(&lt;1, 7)</td>
</tr>
<tr>
<td>p-value vs. Control</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Phase III: BEACON Study

Waterfall Plots of Best Change in Sum of Diameters (based on central review)

*Patients whose SoD was contraindicated by assessment of PD. SoD=sum of longest diameter. Includes patients with measurable disease with a baseline and at least one post-baseline scan.

Tabernero J, Van Cutsem….., Kopetz S, ESMO-WCGIC 2019
Non-V600 BRAF mutations

✓ Codon 594/596 kinase activity impaired
✓ Favorable prognosis
✓ L sided
✓ Male > female
✓ Low grade; not mucinous
✓ (+) KRAS mut; (-) MSI
✓ No peritoneal spread
✓ Codon 601/597 similar to V600E

Molecular subtypes in CRC

Can predict response to therapy

- "pan-WT"
- KRAS ex2
- Fusions (e.g. NTRK)
- Amplifications (e.g. HER2)
- KRAS ex3,4
- BRAF
- NRAS
- HER2 amplification
- NTRK fusion
- Trastuzumab + lapatinib
- Larotrectinib

Sartore-Bianchi et al, Lancet Oncology 2016; Drilon et al, NEJM 2018
HER 2 targeted therapy in mCRC

Figure 1. Actionable Molecular Targets in mCRC

Abbreviations: mCRC, metastatic colorectal cancer; wt, wild-type; dMMR, deficient DNA mismatch repair; MSI-H, microsatellite instability-high; mut, mutation

Presented by Michael Overman at 2019 ASCO Annual Meeting

NCCN Guidelines 2019 5/15/19 update
Outcomes have progressively improved with the evolution of metastatic CRC treatment options.

Median OS

- **1980s**: BSC, 5-FU
- **1990s**: Irinotecan, capecitabine, Oxaliplatin, Bevacizumab
- **2000s**: Cetuximab, Panitumumab, Bevacizumab
- **2015**: Aflibercept, Regorafenib, Trifluridine-tipiracil

Sources:
5. Cunningham, …Van Cutsem et al. NEJM 2004
7. Van Cutsem et al. JCO 2007
10. Maier, Van Cutsem et al NEJM 2015

Note: The graph shows a timeline from 1980s to 2015, with a projection to 2030.
Leuven, Belgium

- 25 km east of Brussel: ~ 100,000 inhabitants
- KUL: University founded in 1425: > 58,000 students
- Largest Beer Brewery in world (>25% of world production)
JOIN US IN 2020
1–4 JULY
BARCELONA