How to treat a patient with metastatic CRC?
Towards personalized treatment strategies

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Progress in the treatment of mCRC

- CHEMOTHERAPY: combination of cytotoxic and biological targeted drugs

  **Cytotoxic agents**
  - 5-FU/capecitabine (S1)
  - irinotecan
  - oxaliplatin
  - raltitrexed
  - (mitomycin)
  - Trifluridine/tipiracil

  **Biological agents**
  - bevacizumab
  - cetuximab
  - panitumumab
  - afiblercept
  - ramucirumab
  - regorafenib
  - pembrolizumab
  - nivolumab
  - early: Sym004, dabrafenib, vemurafenib, encorafenib, trametinib, binimetinib, atezolizumab, tremelimumab, cobimetinib, alpelisib, napabucasin, bispecific antibodies (eg: RO6958688: antiCD3-CEA, crossMab RG7716 ...), vantictumab, cabozantinib (nintedanib, MABp1, ....)

- Other contributing factors to improved outcome: surgery, locoregional treatment....
A classical case of mCRC in 2018
CONTINUUM OF CARE

1991: OS 6 months

17th ESO-ESMO Masterclass in Clinical Oncology
The continuum of care of mCRC

1st line cytotoxic

2nd line cytotoxic

3rd line cytotoxic

Surgery (RFA)

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

Maintenance strategy
At progression change chemo, biologic or both?

Independent sequences?

Locoregional therapy: SIRS

1st line biologic

2nd line biologic

3rd line biologic

Bevacizumab/aflibercept/ramucirumab
Cetuximab/panitumumab
Regorafenib
Pembrolizumab/nivolumab

How to start?
What is best strategy?
What to do for liver metastases?
Table 4. Drivers for first-line treatment

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>Patient characteristics</th>
<th>Treatment characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour burden</td>
<td>Age</td>
<td>Toxicity profile</td>
</tr>
<tr>
<td>Tumour localisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour biology</td>
<td>Performance status</td>
<td>Flexibility of treatment administration</td>
</tr>
<tr>
<td>RAS mutation status</td>
<td>Organ function</td>
<td>Socio-economic factors</td>
</tr>
<tr>
<td>BRAF mutation status</td>
<td>Comorbidities, patient attitude, expectation and preference</td>
<td>Quality of life</td>
</tr>
</tbody>
</table>

Figure 1 | Proposed landscape of molecularly targeted treatments for metastatic colorectal cancer. The schematic summarizes the biomarker-based treatment options available and the typical proportions of patients in each biomarker subgroup. FOLFOXIRI, 5-fluorouracil, folinic acid, oxaliplatin, and irinotecan; MSI, microsatellite instability; mut, mutant, PD-1, programmed cell-death protein 1; wt, wild type.

Molecular aberrations in mCRC

Patients with unresectable liver metastases: OS is the primary treatment goal

Classification

Upfront resectable

10%

Borderline resectable

20%

Unresectable

70%

Resection

CT ± biologic

≈12%¹

CT ± biologic

Relapse

14%²

4%

Overall survival / long-term disease control

96%

CT

Treatment strategy

Curative surgery

Required outcome


- In situations where the criteria for prognosis and resectability are not sharply defined, perioperative therapy should be considered (as part of a continuum of treatment option) [IV, B] (Figure 2). Patients with synchronous onset of metastases should be allocated to this group and therapeutic pathway.

- In patients with favourable oncological and technical (surgical) criteria, who have not received perioperative chemotherapy, there is no strong evidence to support the use of adjuvant chemotherapy [II, C], whereas patients with unfavourable criteria may benefit from adjuvant treatment [III, B].

- In patients who have not received any previous chemotherapy, adjuvant treatment with FOLFOX or CAPOX is recommended (unless patients were previously recently exposed to oxaliplatin-based adjuvant chemotherapy) [IV, B].

- Decision-making should include patients’ characteristics and preferences [IV, B].
Patients with unresectable liver metastases: OS is the primary treatment goal

- **Classification**
  - Upfront resectable: 10%
  - Borderline resectable: 20%
  - Unresectable: 70%

- **Treatment strategy**
  - Resection
    - Curative surgery: 4%
    - CT ± biologic: ≈8%
  - Overall survival / long-term disease control: 96%

- **Relapse**
  - CT ± biologic: ≈12%

- **Required outcome**
  - Curative surgery

Recommendation 13: conversion therapy.

- In potentially resectable patients (if conversion is the goal), a regimen leading to high RRs and/or a large tumour size reduction (shrinkage) is recommended [II, A].
- There is uncertainty surrounding the best combination to use as only few trials have addressed this specifically:
  - In patients with RAS wild-type disease, a cytotoxic doublet plus an anti-EGFR antibody seems to have the best benefit risk/ratio, although the combination of FOLFOXIRI plus bevacizumab may also be considered and, to a lesser extent, a cytotoxic doublet plus bevacizumab [II, A].
  - In patients with RAS-mutant disease: a cytotoxic doublet plus bevacizumab or FOLFOXIRI plus bevacizumab [II, A].
- Patients must be re-evaluated regularly in order to prevent the overtreatment of resectable patients as the maximal response is expected to be achieved after 12–16 weeks of therapy in most patients.

Online Ann Oncol, July 2016
Treatment of metastatic disease

Assessment of clinical condition of the patient

**FIP**

**Unit** (but may be suitable)

**FP + bevacizumab; reduced dose oxaliplatin; anti-EGFR**

**ESMO**

Patients with clearly resectable metastases

Surgery alone

Surgery with perioperative postoperative CT

MOLECULAR PROFILE

OMD

Cyto-reduction (Shrinkage) **

Disease control (control of progression)

MOLECULAR PROFILE

RAS **

RAS **

BRAF **

CT doublet + anti-EGFR

CT doublet + anti-EGFR

CT triplet + bevacizumab

CT triplet + bevacizumab

CT triplet + bevacizumab

Clinical benefit on an experimental, continues

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

Progressive disease

Second-line

Surgery

Continue

Continue; maintenance; or pause

Progressive disease

Second-line

Continue; maintenance; or pause

## Treatment of metastatic disease

<table>
<thead>
<tr>
<th>Patient’s classification</th>
<th>‘Fit’ patients</th>
<th>‘Unfit’ patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>A) Conversion and achievement of NED</td>
<td>Asymptomatic patients</td>
</tr>
<tr>
<td></td>
<td>B) Impending clinical threat, impending organ dysfunction and severe (disease-related) symptoms</td>
<td>No impending clinical threat</td>
</tr>
<tr>
<td></td>
<td>Treatment biomarker driven: RAS wt, RAS mt, BRAF mt patient subgroups</td>
<td>Resection not an option</td>
</tr>
<tr>
<td><strong>Treatment goal</strong></td>
<td>A) Cytoreduction, followed by R0 resection: NED achieved by LAT</td>
<td>Treatment biomarker driven: RAS wt, RAS mt, BRAF mt patient subgroups</td>
</tr>
<tr>
<td></td>
<td>B) Improvement of symptoms and hence avoidance of rapid evolution and prolonged survival</td>
<td>Disease control and hence prolonged survival</td>
</tr>
<tr>
<td></td>
<td>LAT, local and ablative therapy; mt, mutant; NED, no evidence of disease; wt, wild-type.</td>
<td>Palliative</td>
</tr>
</tbody>
</table>

Online Ann Oncol, July 2016
Oncogenic activation of the EGFR signaling pathway in mCRC

Antibodies (cetuximab, panitumumab)

HER2 amplified

Targeted agents in BRAF mt

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

Increasing relative proportion of wild (wt) population responsive to EGFR mAbs

Detection of additional mutant tumors that are resistant to EGFR mAbs (cetuximab, panitumumab)

Enhanced benefit profile for EGFR inhibitors in the more selected population
Anti-angiogenic Agents: Different Mechanisms of Action and Different Targets

- Anti-angiogenesis is multifactorial
- VEGF-A, VEGF-B, VEGF-C, VEGF-D, PIGF, and their receptors VEGFR-1, VEGFR-2, and VEGFR-3 are the major mediators of angiogenesis
- VEGF-A primarily interacts with VEGFR-1 and VEGFR-2
- VEGF-A binds to VEGFR-2 with the highest relative affinity
- PIGF and VEGF-B interact with VEGFR-1
- No predictive marker for angiogenesis

Head to Head-Meta-Analysis based on three phase 2/3 RCTs in the first-line setting of mCRC patients.

<table>
<thead>
<tr>
<th>Trials, which were considered in the meta-analysis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRE-3(^2) (Phase 3)</td>
</tr>
<tr>
<td><strong>KRAS-WT mCRC(^1)</strong> (n = 592)</td>
</tr>
<tr>
<td>Cetuximab + FOLFIRI</td>
</tr>
<tr>
<td>Bevacizumab + FOLFIRI</td>
</tr>
<tr>
<td><strong>KRAS-WT mCRC(^1)</strong> (n = 285)</td>
</tr>
<tr>
<td>Panitumumab + mFOLFOX6</td>
</tr>
<tr>
<td>Bevacizumab + mFOLFOX6</td>
</tr>
<tr>
<td><strong>KRAS-WT mCRC(^1)</strong> (n = 1137)</td>
</tr>
<tr>
<td>Cetuximab + FOLFOX/FOLFIRI</td>
</tr>
<tr>
<td>Bevacizumab + FOLFOX/FOLFIRI</td>
</tr>
<tr>
<td>Ein dritter Bevacizumab + Cetuximab + FOLFOX/FOLFIRI Studienarm wurde am 10.09.2009 geschlossen</td>
</tr>
</tbody>
</table>

\(^1\)Retrospektive RAS-Analyse

\(^2\)Phase 3

\(^3\)Phase 2

\(^4\)CALGB/SWOG 80405

\(^5\)Phase 3

Metaanalysis: Head to Head studies of anti-VEGF vs anti-EGFR therapy in first line RAS-WT mCRC


OS in RAS-WT Patients, per trial and total

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% KI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRE-3</td>
<td>0.70 (0.53–0.92)</td>
<td>37.01</td>
</tr>
<tr>
<td>PEAK</td>
<td>0.63 (0.39–1.02)</td>
<td>15.87</td>
</tr>
<tr>
<td>CALGB</td>
<td>0.90 (0.70–1.10)</td>
<td>47.12</td>
</tr>
<tr>
<td>total</td>
<td>0.77 (0.63–0.95)</td>
<td>100.00</td>
</tr>
<tr>
<td>p= 0.016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS and ORR in RAS-WT Patients, total

<table>
<thead>
<tr>
<th></th>
<th>HR (95% KI)</th>
<th>% Weight</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.92 (0.71–1.18)</td>
<td>100</td>
<td>0.50</td>
</tr>
<tr>
<td>ORR</td>
<td>1.46 (1.13–1.90)</td>
<td>100</td>
<td>0.004</td>
</tr>
</tbody>
</table>

A first line anti-EGFR-strategy in patients with mCRC and RAS-WT status might be superior in terms of OS and ORR compared to anti-VEGF-based treatment

2014 patients
Midgut vs Hindgut: Right vs Left

**Right-sided (proximal) colon cancer**
- More common in women
- Microsatellite instability
- Derived from midgut
- CIMP+, BRAF mutation
- MAPK signaling, serrated pathway
- Mutagenic CYP450 metabolites
- HNPCC

**Left-sided (distal) colon cancer**
- More common in men
- Chromosomal instability
- Derived from hindgut
- APC, K-ras, DCC, p53 mutations
- EGFR signaling, Wnt signaling
- HER1, HER2 amplification
- FAP

Summary of common clinical and molecular characteristics of right- and left-sided colon tumors and associations with dietary factors. CIMP = CpG island methylator phenotype; HNPCC = hereditary non-polyposis colorectal cancer; APC = adenomatous polyposis coli; K-ras = Kirsten-ras; DCC = deleted in colorectal cancer; FAP = familial adenomatous polyposis.

World J Gastroenterol. May 7, 2015; 21(17): 5167-5175
Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials†

D. Arnold¹, B. Lueza², J.-Y. Douillard³, M. Peeters⁴, H.-J. Lenz⁵, A. Venook⁶, V. Heinemann⁷, E. Van Cutsem⁸, J.-P. Pignon², J. Tabernero⁹, A. Cervantes¹⁰,¹¹ & F. Ciardiello¹²*
Figure 2. Forest plots for the prognostic analyses of tumour location (right versus left side) in the control and experimental arms (chemotherapy plus EGFR antibody therapy) for—overall survival, (A) and (B), respectively, progression-free survival, (C) and (D), respectively, and objective response rate, (E) and (F), respectively. CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NA, not available; OR, odds ratio.
Figure 3. Forest plots for predictive analyses of tumour location (right versus left side) in trials comparing chemotherapy plus EGFR antibody therapy (experimental arm) with chemotherapy alone or chemotherapy plus bevacizumab (control arm)—(A) overall survival, (B) progression-free survival and (C) objective response rate. CI, confidence interval; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; NA, not available; OR, odds ratio.
Figure 3. Forest plots for predictive analyses of tumour location (right versus left side) in trials comparing chemotherapy plus EGFR antibody therapy (experimental arm) with chemotherapy alone or chemotherapy plus bevacizumab (control arm)—(A) overall survival, (B) progression-free survival and (C) objective response rate. CI, confidence interval; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; NA, not available; OR, odds ratio.
Primary Tumor Location and Potential Treatments

**Right-sided**
- MSI-H
- BRAF MT
- ↑KRAS MT

**Left-sided**
- HER2+
- HER2-targeted agents
- ↑KRAS WT
- ↑AREG/EREG

**Treatments**
- Bevacizumab + CT
- Anti-EGFRs + CT
- Anti-PD1
- Bev + Triplet CT

References:
- Brule SY, et al. ASCO 2013. Abstract 3528;

17th ESO-ESMO Masterclass in Clinical Oncology
## Preferred choices

<table>
<thead>
<tr>
<th>Goal / condition</th>
<th>Molecular</th>
<th>Prefered 1st line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytoreduction</td>
<td>all WT</td>
<td>Left: Doublet/EGFR Right: FOLFOX/beva or FOLFOXIRI/beva or doublet/EGFR</td>
</tr>
<tr>
<td></td>
<td>RAS mut</td>
<td>FOLFOX/beva or FOLFOXIRI/beva</td>
</tr>
<tr>
<td></td>
<td>BRAF mut</td>
<td>FOLFOXIRI/beva or doublet/beva</td>
</tr>
<tr>
<td>Disease stabilization</td>
<td>all WT</td>
<td>Left: Doublet/EGFR Right: Doublet/beva</td>
</tr>
<tr>
<td></td>
<td>RAS mut</td>
<td>Doublet/beva</td>
</tr>
<tr>
<td></td>
<td>BRAF mut</td>
<td>Doublet/beva or FOLFOXIRI/beva</td>
</tr>
<tr>
<td>„frail“, or chosen sequential treatment</td>
<td>no BRAF !</td>
<td>Capecitabine/beva</td>
</tr>
</tbody>
</table>

Arnold D, ... Van Cutsem et al. Ann Oncol 2017
Recommendation 19: Maintenance therapy

- Patients receiving FOLFOX or CAPOX plus bevacizumab-based therapy as induction therapy, should be considered for maintenance therapy after 6 cycles of CAPOX or 8 cycles of FOLFOX. The optimal maintenance treatment is a combination of a fluoropyrimidine (plus bevacizumab). Bevacizumab as monotherapy is not recommended [I, B].
- Patients receiving FOLFIRI can continue on induction therapy – at a minimum – for as long as tumour shrinkage continues and the treatment is tolerable [V, B].
- For patients receiving initial therapy with FOLFOXIRI plus or minus bevacizumab a fluoropyrimidine plus bevacizumab may be considered as maintenance therapy.
- For patients receiving initial therapy with single-agent fluoropyrimidine (plus bevacizumab), induction therapy should be maintained [V, A]. Individualisation and discussion with the patient is essential [V, A].
- Initial induction therapy or a second-line therapy have to be reintroduced at radiological or first signs of symptomatic progression. If a second-line therapy is chosen, re-introduction of the initial induction treatment should be a part of the entire treatment strategy as long as no residual toxicity is present [III, B].
Treatment of metastatic disease

**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>Fit patients[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment goal</td>
<td>Cytoreduction (tumour shrinkage)</td>
</tr>
<tr>
<td>Molecular profile</td>
<td>RAS wt</td>
</tr>
<tr>
<td>Second line</td>
<td>CT doublet + bevacizumab</td>
</tr>
<tr>
<td>Preferred choice(s)</td>
<td>FOLFIRI + aflibercept/ramucirumab</td>
</tr>
<tr>
<td>Second choice</td>
<td>FOLFIRI + aflibercept/ramucirumab</td>
</tr>
</tbody>
</table>

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].
Targeting the RAF pathway in mCRC

Signaling in BRAF mt CRC

Reactivation of EGFR signaling upon BRAF inhibition

BRAF inhibitors for BRAF mt mCRC: Triple combinations

<table>
<thead>
<tr>
<th>BRAF inhibitor</th>
<th>EGFR inhibitor</th>
<th>MEK inhibitor</th>
<th>or</th>
<th>PI3K/AKT inhibitor</th>
<th>or</th>
<th>Chemo-therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + vemurafenib + irinotecan (n=17)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cetuximab + encorafenib + alpelisib (n=28)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Panitumumab + dabrafenib + trametinib (n=35)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRAF inhibitor-containing combination (n)</th>
<th>ORR, %</th>
<th>SD, %</th>
<th>Median PFS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + vemurafenib + irinotecan (n=17)</td>
<td>35</td>
<td>59</td>
<td>7.7</td>
</tr>
<tr>
<td>Cetuximab + encorafenib + alpelisib (n=28)</td>
<td>32</td>
<td>61</td>
<td>4.3</td>
</tr>
<tr>
<td>Panitumumab + dabrafenib + trametinib (n=35)</td>
<td>26</td>
<td>57</td>
<td>4.1</td>
</tr>
</tbody>
</table>

1. Hong DS, et al. ASCO 2015 (Abstract No. 3511);
2. Elez E, et al. WCGC 2015 (Abstract No. LBA08);
Phase III: BEACON Study: lead in part

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

Van Cutsem E et al, ASCO GI 2018
Phase III: BEACON Study

**SAFETY LEAD-IN**
Safety and tolerability will be assessed in patients receiving binimetinib, encorafenib, and cetuximab for the treatment of BRFafV600E-mutant metastatic colorectal cancer.

**PHASE III OUTLINE**

**RANDOMIZED PORTION**

**Patient population**
- BRFafV600E mutant
- 1-2 prior regimens in metastatic setting
- N=415

**RANDOMIZATION**

**ARM A**
- binimetinib + encorafenib + cetuximab
- n=205

**ARM B**
- encorafenib + cetuximab
- n=205

**ARM C**
- FOLFIRI or irinotecan + cetuximab
- n=205

**OTHER SECONDARY OBJECTIVES**

- To compare overall response rate (ORR) and progression-free survival (PFS) in Arm A vs Arm C
- To compare ORR and PFS in Arm B vs Arm C
- To compare OS in Arm A vs Arm B

**CONFIRMED FOLLOW-UP FOR EVALUATION OF OS**

**PRIMARY OBJECTIVE**
To compare OS in Arm A vs Arm C

**KEY SECONDARY OBJECTIVE**
- To compare OS in Arm B vs Arm C

*FOLFIRI*: 5-fluorouracil bolus followed by continuous infusion + leucovorin + irinotecan.

Mismatch-repair status predicted clinical benefit of immune checkpoint blockade in CRC

Treatment with pembrolizumab (anti-PD-1 antibody)
(n=11 mismatch repair-deficient CRC, n=21 mismatch-repair proficient CRC, n=9 mismatch-repair deficient non-CRC)

Radiographic responses*

Immune-related ORR in mismatch-repair deficient vs proficient CRC: 40% vs 0%

Adjusted OS HR for mismatch-repair deficient vs proficient CRC: 0.18, p=0.05

OS in CRC

First defined by Papadopoulo and Vogelstein in early 1990s.

Durable Responses in Phase II Studies with PD antibodies in MSI-H

Pembrolizumab

Nivolumab

1 year

Le. ASCO, 2015

Overman ASCO, 2016

26% PR + 30% durable SD

Presented By Neil Segal at 2016 ASCO Annual Meeting
Durable Responses with nivolumab + ipilimumab in MSI-H 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.

Overman M….Van Cutsem E et al, J Clin Onc 2018
Regorafenib inhibits VEGFR1, VEGFR2, VEGFR3 and other Pathways, including RET, KIT, PDGFRα, PDGFRβ, FGFR1, FGFR2, TIE2, BRAF, BRAF

Inhibition by regorafenib

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

F₃dT (FTD)
Thymidine-based nucleoside analogue

Inhibition of tumor growth
DNA dysfunction
FTD incorporation into DNA

FTD: Trifluridine
TPI: Tipiracil-HCl

Molar ratio = 1 : 0.5
Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial

Axel Grothey*, Eric Van Cutsem*, Alberto Sobrero, Salvatore Siena, Alfredo Falcone, Marc Ychou, Yves Humblot, Olivier Bouché, Laurent Mineur, Carla Barone, Antoine Adenis, Josep Tabernero, Takayuki Yoshino, Heinz-Josef Lenz, Richard M Goldberg, Daniel J Sargent, Frank Chan, Lisa Cunk, Andrea Wagner, Dirk Laurent, for the CORRECT Study Group†

Interpretation Regorafenib is the first small-molecule multikinase inhibitor with survival benefits in metastatic colorectal cancer which has progressed after all standard therapies. The present study provides evidence for a continuing role of targeted treatment after disease progression, with regorafenib offering a potential new line of therapy in this treatment-refractory population.

CONCLUSIONS
In patients with refractory colorectal cancer, TAS-102, as compared with placebo, was associated with a significant improvement in overall survival. (Funded by Taiho Oncology–Taiho Pharmaceutical; RE COURSE ClinicalTrials.gov number, NCT01607957.)
Regorafenib and trifluridine/tipiracil in refractory mCRC:

**CORRECT:** regorafenib

**RE COURSE:** trifluridine/tipiracil

Optimal Sequence in chemorefractory patients?

Considerations:

- Regorafenib: more patients with long term benefit?
- Trifluridine/tipiracil: more favourable safety patterns, but ?? if compared to lower dose of regorafenib
New Molecular Subtypes in Colorectal Cancer May Help to Predict Response to Therapies

Colorectal cancer subtypes: CMS

MSI Immune (14%)
- MSI, CIMP high, hypermethylation
- *BRAF* mutations
- Immune infiltration/activation
- Worse survival after relapse

Canonical (37%)
- SCNA high
- WNT and MYC activation

Mesenchymal (23%)
- SCNA high
- Stromal infiltration, TGF-β activation, angiogenesis
- Worse relapse-free and overall survival

Metabolic (13%)
- Mixed MSI status, SCNA low, CIMP low
- KRAS mutations
- Metabolic deregulation

CMS: consensus molecular subtypes

**CRC subtypes**

**Figure 1 | Schematic representation of CRC subtypes.** Microsatellite instability (MSI) is linked to hypermutation, hypermethylation, immune infiltration, activation of RAS, BRAF mutations, and locations in the proximal colon. Tumours with chromosomal instability (CIN) are more heterogeneous at the gene-expression level, showing a spectrum of pathway activation ranging from epithelial canonical (consensus molecular subtype 2 (CMS2)) to mesenchymal (CMS4). Tumours with CIN are mainly diagnosed in the left colon or rectum, and their microenvironment is either poorly immunogenic or inflamed, with marked stromal infiltration. A subset of CRC tumours enriched for RAS mutations has strong metabolic adaptation (CMS3) and intermediate levels of mutation, methylation and copy number events. EGFR, epidermal growth factor receptor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

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**Press Key Points**

- MSI
- CIN
- CMS1
- CMS2
- CMS3
- CMS4
- RAS and BRAF mutations
- Highly immunogenic
- Inflamed (immune-tolerant)
- Poorly immunogenic
- Adaptative
- Innate
- Proximal
- Distal
- (Tumour location)

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Dienstmann R et al, Nat Rev Cancer, 2017
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