Systemic treatment in advanced disease of colon cancer

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Conflict of interest disclosure:

• **Consultant or Advisory Board:**
  Amgen; Lilly; Bayer; Servier

• **Research grant:**
  Bayer

• **Honoraria:**
  Lilly; Amgen; Bayer; Servier
Advanced colorectal cancer: an impressive progress after 30 years of clinical research

5% vs 25%
How have we got this advancement across these years?

• The recognition of advanced colorectal cancer patients as an heterogeneous population according to disease (site and timing of metastases; resectability or not) and patient characteristics (age; PS)

• The integration of different treatments: surgery; chemotherapy; target therapy, ....

• The identification of the tumor molecular features (RAS/BRAF; and others)
The patients with liver metastases: a heterogeneous population

<table>
<thead>
<tr>
<th>Resectable</th>
<th>Potentially Resectable</th>
<th>Unresectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Biologically challenging</td>
<td>Technically challenging</td>
</tr>
<tr>
<td>- Single M+ - Size ≤ 5 cm - N0 at primary tumor - Metachronous - CEA ≤ 100 ng/mL</td>
<td>- Multiple metastases - Size &gt; 5 cm - N+ at primary tumor - Synchronous metastases - CEA &gt; 100 ng/mL</td>
<td>- Close to hepatic veins or portal branches - Major hepatectomy required</td>
</tr>
</tbody>
</table>

Surgery | Peri-operative chemotherapy + Surgery | Conversion Chemotherapy + Surgery (if sufficient response) | Palliative Chemotherapy

Bittoni A et al, CROH 2013
The Tower of Babel of liver metastases from colorectal cancer: Are we ready for one language?

Resectable metastases

- Single M+
- Size ≤ 5 cm
- N0 at primary tumor
- Metachronous
- CEA ≤ 100 ng/mL

Disease-specific survival (DSS)

- Primary tumor N+
- DFI < 12 months
- >1 metastasis
- Ø >5 cm
- CEA >200 ng/ml

Fong score >2

CRS, clinical risk score; DFI, disease-free interval
The future
a selection based on molecular profile?

FOLFOXIRI/Bevacizumab

Schirripa et al, Br J Cancer '15

Teng, Ann Surg Oncol 2012

Cremolini et al, Eur J Cancer ‘17
The patients with liver metastases: a heterogeneous population

Resectable

- Low Risk
  - Single M+
  - Size ≤ 5 cm
  - N0 at primary tumor
  - Metachronous
  - CEA ≤ 100 ng/mL

- Biologically challenging
  - Multiple metastases
  - Size > 5 cm
  - N+ at primary tumor
  - Synchronous metastases
  - CEA > 100 ng/mL

Potentially Resectable

- Technically challenging
  - Close to hepatic veins or portal branches
  - Major hepatectomy required

Unresectable

- Ultimately Resectable
  - >70-80% of liver involvement
  - < 25% remnant after resection
  - 6 segments involved

- Never resectable
  - Unresectable extrahepatic disease

Surgery

- Peri-operative chemotherapy + surgery

Conversion Chemotherapy + surgery (if sufficient response)

Palliative Chemotherapy

Bittoni A et al, CROH 2013
Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

Biologically challenging
- Multiple metastases
- Size > 5 cm
- N at primary tumor
- Synchronous metastases
- CEA > 100 ng/mL

Technically challenging
- Close to hepatic veins or portal branches
- Major hepatectomy required

Potentially Resectable

A test of time?
Synchronous metastases: one more question, the primary tumour management

- Metastases:
  - Liver limited versus other sites +/-liver?
  - Resectable versus borderline/nonresectable?
  - If resectable then which operative strategy?

- Primary first vs liver first vs synchronous?

- Primary tumour:
  - Symptomatic versus asymptomatic?
  - Easily versus borderline/difficult resectable?
  - Colon versus rectal primary?
Resection of primary tumor and OS: ARCAD database

Individual patient data from 3423 pts in 8 randomized first-line trials

Also after adjustment for prognostic factors and a multivariate analysis OS in the unresected group remained significantly worse (HR: 1.64 95% CI 1.43-1.78)

van Rooijen et al. EJC 2018
# Ongoing Studies of Surgery on Primary Tumor

<table>
<thead>
<tr>
<th>Regimen</th>
<th>CAIRO4 $^{1}$ n=360</th>
<th>GRECCA R8 $^{2}$ n=290</th>
<th>SYNCHRONOUS $^{3}$ n=522</th>
<th>CLIMAT4 $^{4}$ n=278</th>
<th>NCT02149784 $^{5}$ n=480</th>
<th>NCT02291744 $^{6}$ n=130</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PTR-&gt;5FU+Bev Chemo vs 5FU+Bev Chemo</td>
<td>PTR-&gt;Chemo vs Chemo±bev</td>
<td>PTR-&gt;Chemo vs Chemo</td>
<td>PTR-&gt;Chemo vs Chemo</td>
<td>Chemo vs Chemo-&gt;PTR</td>
<td>XELOX vs XELOX-&gt;PRT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>III</th>
<th>III</th>
<th>III</th>
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<th>III</th>
<th>II</th>
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</table>

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>OS</th>
<th>OS</th>
<th>OS</th>
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<th>OS</th>
<th>TFS</th>
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</table>

<table>
<thead>
<tr>
<th>Site</th>
<th>Colorectal</th>
<th>Rectum</th>
<th>Colon</th>
<th>Colon or rectal</th>
<th>Colon</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Status</th>
<th>Recruiting</th>
<th>Recruiting</th>
<th>Recruiting</th>
<th>Recruiting</th>
<th>NA</th>
</tr>
</thead>
</table>

|--------------------------------|----------|----------|----------|-----------|----------|----------|

5ClinicalTrials.gov Identifier: NCT02149784
6. ClinicalTrials.gov Identifier: NCT02291744
Technically challenging liver metastases: The benefit of a tumor shrinkage

**Potentially Resectable**

**Technically challenging**
- Close to hepatic veins or portal branches
- Major hepatectomy required

The best regimen in terms of anatomical response

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response rate</th>
<th>Side effects (3/4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOXIRI/Beva</td>
<td>65%</td>
<td>diarrhea</td>
</tr>
<tr>
<td>FOLFOXIRI/Panitumumab</td>
<td>85%</td>
<td>Skin; diarrhea</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>60%</td>
<td>diarrhea</td>
</tr>
</tbody>
</table>
The patients with liver metastases: a heterogeneous population: clinical

- Resectable
- Potentially Resectable
- Unresectable

Low Risk
- Single M+
- Size ≤ 5 cm
- N0 at primary tumor
- Metachronous
- CEA ≤ 100 ng/mL

Biologically challenging
- Multiple metastases
- Size > 5 cm
- N+ at primary tumor
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Ultimately Resectable
- >70-80% of liver involvement
- <25% remnant after resection
- 6 segments involved

Never resectable
- Unresectable extrahepatic disease

Surgery

Peri-operative Chemotherapy + Surgery

Conversion Chemotherapy + Surgery (if sufficient response)

Palliative Chemotherapy

Bittoni A et al, CROH 2013
184 patients with initially unresectable CRLM
From April 1988 through July 2002

Mean number of lesions: 5.3 metastases
76% bilobar
27% extrahepatic disease

74% Surgery after one line of CT
26% Surgery after 2 or more lines of CT

Overall Survival rates:
5-years: 33%
10-year: 27%

Of 148 patients with a follow-up ≥ 5 years:
16% cured (mean follow-up, 118.6 months)
25% of whom were considered cured after repeat resection of recurrence.

Predictors of cure at Multivariate analysis:
• Maximum size < 30 mm at diagnosis
• Number of metastasis ≤ 3
• Complete pathologic response

Cure can be achieved overall in 16% of patients with initially unresectable CLM resected after downsizing chemotherapy.
What Do We Expect from an Ideal Conversion Chemotherapy?

• High (anatomical) response rate in a short time (relatively)

• Good toxicity profile
  - No hepatotoxicity
  - No interference with surgery
  - No interference with liver regeneration
The best regimen. Does it exist?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response rate</th>
<th>Resection rate</th>
<th>Side effects (3/4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX/FOLFIRI</td>
<td>50%</td>
<td>20-30%</td>
<td>Neuropathy/diarrhea</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>60%</td>
<td>35%</td>
<td>diarrhea</td>
</tr>
<tr>
<td>FOLFIRI/FOLFOX/Beva</td>
<td>35-45%</td>
<td>4%</td>
<td>Diarrhea; neuropathy</td>
</tr>
<tr>
<td>FOLFOXIRI/Beva</td>
<td>65%</td>
<td>40% (LO)</td>
<td>diarrhea</td>
</tr>
<tr>
<td>FOLFIRI/FOLFOX cetuximab/panitumumab</td>
<td>57%</td>
<td>30-38% (LO)</td>
<td>Skin; diarrhea</td>
</tr>
<tr>
<td>FOLFOXIRI/Panitumumab</td>
<td>85%</td>
<td>70 LO)</td>
<td>Skin; diarrhea</td>
</tr>
</tbody>
</table>
Molecular features are crucial points

- RAS WT; BRAF WT  
  EGFR based regimen
- RAS mut or B-RAF mut  
  FOLFOXIRI/Beva

But keep in our mind that ....

The higher the Number of lines...

The more prolonged the Chemo...

The lower the Survival after liver resection...
The patients with never resectable metastases: A different perspective

Not only the most effective regimen but rather the best sequence of the available regimens (from first to second and further lines)

The continuum of care for the best survival opportunity

Bittoni A et al, CROH 2013
How to choose the 1° line treatment:

- Molecular: RAS/BRAF
- Clinical: right vs left
- Sequences
  - Regulatory rules
  - Patients: PS; age
  - Objective: resection of metastases/survival

what we have to do
what we can do
what we can pursue
1st line treatment of mCRC: ESMO consensus guidelines

Assessment of clinical condition of the patient

Fit\(^a\)

Unfit\(^a\) (but may be suitable)

Unfit\(^a\)

GOAL

Cytoreduction (Shrinkage)**

OMD
See figure 2

MOLECULAR PROFILE

RAS wt

RAS mt

BRAF mt

CT doublet + anti-EGFR

Combination CT + bevacizumab

CT triplet + bevacizumab

Disease control (control of progression)

MOLECULAR PROFILE

RAS wt

RAS mt

BRAF mt

CT doublet + biological agent

CT doublet + bevacizumab

CT triplet +/- bevacizumab

Van Cutsem et al., Ann Oncol ‘17
Treatment algorithm based on molecular and clinical features for fit patients

1° line

MUT

RAS/BRAF WT

B-RAF

RAS

FOLFOXIRI/BEVA
The BRAF mutated tumors

Van Cutsem  J Clin Oncol  '11

**BRAF mut**

HR: 0.908, p=0.74

<table>
<thead>
<tr>
<th></th>
<th>Pmab+ FOLFOX</th>
<th>FOLFOX</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT RAS</td>
<td>15.6</td>
<td>19.2</td>
<td>1.25</td>
<td>0.04</td>
</tr>
<tr>
<td>MT BRAF</td>
<td>10.5</td>
<td>9.2</td>
<td>0.90</td>
<td>0.76</td>
</tr>
<tr>
<td>WT RAS</td>
<td>26.0</td>
<td>20.2</td>
<td>0.78</td>
<td>0.04</td>
</tr>
<tr>
<td>WT RAS and <strong>BRAF</strong></td>
<td>28.3</td>
<td>20.9</td>
<td>0.74</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial

The BRAF “narrative”

Phase II prospective trial of FOLFOXIRI plus bev in *BRAF* mutant mCRC patients

Median PFS: 9.2 months
(95%CI 5.1-13.3)

<table>
<thead>
<tr>
<th>N</th>
<th>FOLFIRI + bev Median OS</th>
<th>FOLFOXIRI + bev Median OS</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAS and BRAF wt</strong></td>
<td>93</td>
<td>33.5</td>
<td>41.7</td>
</tr>
<tr>
<td><strong>RAS mutated</strong></td>
<td>236</td>
<td>23.9</td>
<td>27.3</td>
</tr>
<tr>
<td><strong>BRAF mutated</strong></td>
<td>28</td>
<td>10.7</td>
<td>19.0</td>
</tr>
</tbody>
</table>
The treatment for B-RAF mutant tumours: no more chemotherapy?

- RECIST Response: 43%
- Median PFS: 8.0 mos

Van Cutsem et al, ASCO GI Symposium 2018
Treatment algorithm based on molecular and clinical features for fit patients

MUT

1° line

B-RAF

FOLFOXIRI/BEVA

RAS

FOLFOX/FOLFIRI
BEVA
FOLFOXIRI/BEVA

RAS mutated tumours:
The choice of cytotoxic drugs
Biological agents: bevacizumab
Hurwitz, Kabinavar, .....
Treatment algorithm based on molecular and clinical features for fit patients

1° line

- **MUT**
  - B-RAF
  - RAS
  - FOLFOXIRI/BEVA

- **WT BRAF/RAS**

- FOLFOX/FOLFIRI
  - BEVA
  - FOLFOXIRI/BEVA
An old question in RAS/BRAF wt:
The best targeted agents to be used in first line
A study-level meta-analysis of efficacy data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in patients with RAS wild-type metastatic colorectal cancer

Volkert Heinemann, Fernando Rivera, Bert H. O’Neil, Sebastian Stintzing, Rejia Koukakis, Jan-Henrik Terwey,

<table>
<thead>
<tr>
<th>Study</th>
<th>HR [95% CI]</th>
<th>p-value</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB (N=526)</td>
<td>0.90 [0.80, 1.01]</td>
<td>0.13</td>
<td>45.4</td>
</tr>
<tr>
<td>FIRE-3 (N=400)</td>
<td>0.80 [0.60, 1.05]</td>
<td>0.12</td>
<td>17.7</td>
</tr>
<tr>
<td>PEAK (N=170)</td>
<td>0.87 [0.75, 1.01]</td>
<td>0.06</td>
<td>27.1</td>
</tr>
</tbody>
</table>

A Forest plot showing meta-analysis results for (A) overall survival, (B) progression-free survival (RAS wild-type population). Weight is relative weight (%) from the fixed-effect model. p-value is two sided. CI, confidence interval; EGFR, epidermal growth factor receptor inhibitor; HR, hazard ratio; N, total study size; n, total number evaluable; n1, number evaluable in the EGFR arm; n2, number evaluable in the bevacizumab arm.

FOLFIIRI plus cetuximab versus FOLFIIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial


Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial

Alan P. Venook, MD, Gonzalo Menezes, PhD, Heiko-Josef Lenz, MD, Federico Innocenzi, Brien Frith, BS, Jeffrey A. Meyerhardt, MD, MPH, Deborah J. Schrag, MD, MPH, Clelia Georgoulis, MD, H. C. O’Byrne, MD, James N. Kemeny, MD, Scott Berry, MD, MD, MS, FACP, ASCO, MD, Public, MD, Eugene M. Oldridge, MD, Richard M. Goldberg, MD, Howard S. Hochman, MD, Richard L. Schilsky, MD, Monica M. Berek, MD, Anthony E. Di Paola, MD, Peter Watson, MD, R.E. Benson III, MD, Daniel L. Mulligan, MD, Robert J. Mayer, MD, Charles Blanke, MD, FACP.

PEAK: A Randomized, Multicenter Phase II Study of Panitumumab Plus Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab Plus mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer

Lee S. Schwartzberg, Fernando Rivera, Michael Parkhous, Coopmio Pavola, Juan-Luc Cancr, J. Randolph Houl, Hua Yu, Kelly S. Oliver, and William Y. Go
Current evidence to suggest anti-VEGF followed by anti-EGFR is sub-optimal: preclinical
Current evidence to suggest anti-VEGF followed by anti-EGFR is sub-optimal: clinical
Another question:
Does primary tumor sidedness matter?
Prognostic impact

1.437.846 patients in 66 studies (stage I→IV)

HR (left vs right): 0.82 [95%CI: 0.79-0.84], p<0.001

STRATIFY CLINICAL TRIALS
Predictive impact – bev versus anti-EGFRs

### Left-sided

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB/SWOG 80405</td>
<td>325</td>
<td>0.77</td>
<td>(0.59, 0.99)</td>
<td>0.0003</td>
</tr>
<tr>
<td>FIRE-3</td>
<td>306</td>
<td>0.63</td>
<td>(0.48, 0.85)</td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>107</td>
<td>0.84</td>
<td>(0.22, 3.27)</td>
<td></td>
</tr>
</tbody>
</table>

Summary (FE): 0.71 (0.58, 0.85) 0.0003
Summary (RE): 0.71 (0.58, 0.85) 0.0003

Heterogeneity: I² = 0%, 95% CI = (0%, 95.1%)
P-value = 0.575 ($\chi^2$ test)

### Right-sided

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB/SWOG 80405</td>
<td>149</td>
<td>1.36</td>
<td>(0.93, 1.99)</td>
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<tr>
<td>FIRE-3</td>
<td>88</td>
<td>1.31</td>
<td>(0.81, 2.11)</td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>36</td>
<td>0.45</td>
<td>(0.08, 2.49)</td>
<td></td>
</tr>
</tbody>
</table>

Summary (FE): 1.3 (0.97, 1.74) 0.081
Summary (RE): 1.3 (0.97, 1.74) 0.081

Heterogeneity: I² = 0%, 95% CI = (0%, 99.4%)
P-value = 0.468 ($\chi^2$ test)

p for interaction <0.001
Tumour location should be considered for treatment choice in RASwt, B-RAF wt

<table>
<thead>
<tr>
<th>RAS/RAF wt</th>
<th>Treatment guidelines</th>
<th>WCGC 2017</th>
<th>Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESMO(^1)</td>
<td>NCCN(^2)</td>
<td>Axel Grothey(^3)</td>
</tr>
<tr>
<td><strong>Left-sided</strong></td>
<td>EGFR mAbs are Standard of Care in 1st line</td>
<td>No clear preference for EGFR mAbs or bevacizumab in 1st line</td>
<td>EGFR mAbs are preferred, bevacizumab can be used in select patients in 1st line</td>
</tr>
<tr>
<td><strong>Right-sided</strong></td>
<td>EGFR mAbs can be considered in first line if response is goal</td>
<td>No EGFR mAbs in 1st line and potentially not in any line</td>
<td>No EGFR mAbs in 1st line (if response is goal, consider triplet), but allow EGFR mAbs in later line</td>
</tr>
</tbody>
</table>

Treatment algorithm based on molecular and clinical features for fit patients.

1° line

**MUT**

- **B-RAF**
- **RAS**
- **FOLFOXIRI/BEVA**

**WT BRAF/RAS**

- **dx**
- **sx**
- **Cetuximab/panitumumab/chemotherapy**

**1° line**

- **FOLFOX/FOLFIRI**
- **(!) BEVA**
- **FOLFOXIRI/BEVA**
- **FOLFOX/FOLFIRI BEVA**
- **FOLFOXIRI/BEVA**
A critical point: how long have we treat a patient in first line? Or in other words, is maintenance treatment worthwhile?
Maintenance with panitumumab:

VALENTINO: study design

Phase II - non-inferiority

Primary endpoint: 10m-Progression Free Rate

Median Follow Up, months (IQR): 13.8 (8.6-18.3)

HR =1.55; 95% CI: 1.09-2.20; p=0.011

<table>
<thead>
<tr>
<th></th>
<th>10-months PFS Rate</th>
<th>95% CI</th>
<th>Median PFS Months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>62.8%</td>
<td>54.0-73.1</td>
<td>13.0</td>
<td>10.5-16.0</td>
</tr>
<tr>
<td>(S-Fu/LV + pan)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td>52.8%</td>
<td>43.4-64.3</td>
<td>10.2</td>
<td>8.9-12.2</td>
</tr>
<tr>
<td>pan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The second line

MUT

B-RAF

RAS

dx

WT

sx

1° line

FOLFOXIRI/BEVA

FOLFOX/FOLFIRI
BEVA

FOLFOX/FOLFIRI
BEVA

panitumumab

Cetuximab/panitumumab

FOLFOXIRI/BEVA

2° line

?
HOW MANY PATIENTS RECEIVE A SECOND-OR THIRD-LINE THERAPY?

US-Wide Cohort

1-st line
100 % of patients

2°-line
≂ 53%

3°-line
≂ 28%

4°-line
≂ 17%

FIRE 3

1-st line
100 % of patients

2°-line
≂ 69,9 %

3°-line
≂ 43%

Do we have enough evidence to drive 2nd-line treatment decisions?  ESMO guidelines

<table>
<thead>
<tr>
<th>Category</th>
<th>Fit patients&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Cytoreduction (tumour shrinkage)</th>
<th>Disease control (control of progression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular profile</td>
<td>First-line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred choice(s)</td>
<td></td>
<td>CT doublet + EGFR antibody&lt;sup&gt;c&lt;/sup&gt;</td>
<td>FOLOFOXIRI + bevacizumab or CT doublet + EGFR antibody&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Second choice</td>
<td>FOLOFOXIRI + bevacizumab</td>
<td>CT doublet + bevacizumab</td>
<td>CT doublet + bevacizumab</td>
</tr>
<tr>
<td>Third choice</td>
<td>CT doublet + bevacizumab</td>
<td>FOLOFOXIRI</td>
<td>CT doublet + bevacizumab</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td>FP + bevacizumab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>FP + bevacizumab&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Preferred choice</td>
<td></td>
<td>Pause</td>
<td>Pause</td>
</tr>
<tr>
<td>Second choice</td>
<td>FOLOFOXIRI</td>
<td>Pause</td>
<td>Pause</td>
</tr>
<tr>
<td>Second line</td>
<td></td>
<td>FOLOFOXIRI + afiblercept/ ramucirumab</td>
<td>FOLOFOXIRI + afiblercept/ ramucirumab</td>
</tr>
<tr>
<td>Preferred choice(s)</td>
<td></td>
<td>CT doublet + bevacizumab</td>
<td>CT doublet + bevacizumab</td>
</tr>
<tr>
<td>Second choice</td>
<td>CT doublet + EGFR antibody or FOLOFOXIRI + afiblercept/ ramucirumab</td>
<td>FOLOFOXIRI + afiblercept/ ramucirumab</td>
<td>FOLOFOXIRI + afiblercept/ ramucirumab</td>
</tr>
</tbody>
</table>

Treatment algorithm based on molecular and clinical features

MUT

B-RAF

FOLFOXIRI/BEVA

1° line

RAS

FOLFOX/FOLFIRI

FOLFOX/BEVA

FOLFOXIRI/BEVA

dx

sx

2° line

FOLFIRI/Aflibercept

Cetuximab/panitumumab

WT

FOLFOX/FOLFIRI BEVA

FOLFOXIRI/BEVA

panitumumab

?
# BRAF population in the VELOUR trial

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>OS</th>
<th>PFS</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>Aflibercept</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>BRAF wt</strong></td>
<td>446</td>
<td>12.4 (10.7 – 15.1)</td>
<td>13.0 (12.4 – 15.9)</td>
<td>4.5 (4.1 – 5.8)</td>
</tr>
<tr>
<td><strong>HR (95%CI)</strong></td>
<td></td>
<td>0.84 (0.67 – 1.05)</td>
<td>0.76 (0.61 – 0.94)</td>
<td>1.76 (0.99 – 3.14)</td>
</tr>
<tr>
<td><strong>BRAF mutant</strong></td>
<td>36</td>
<td>5.5 (3.5 – 10.6)</td>
<td>10.3 (5.3 – NA)</td>
<td>2.2 (1.4 – 8.3)</td>
</tr>
<tr>
<td><strong>HR (95%CI)</strong></td>
<td></td>
<td>0.42 (0.16-1.09)</td>
<td>0.59 (0.22 – 1.58)</td>
<td>1.26 (0.14 – 11.01)</td>
</tr>
<tr>
<td><strong>Interaction test</strong></td>
<td>0.08</td>
<td>0.29</td>
<td>0.98</td>
<td></td>
</tr>
</tbody>
</table>
Treatment algorithm based on molecular and clinical features

<table>
<thead>
<tr>
<th>MUT (MUTATION)</th>
<th>WT (WILD TYPE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-RAF</td>
<td>RAS</td>
</tr>
<tr>
<td>FOLFOXIRI/BEVA</td>
<td>FOLFOX/FOLFIRI BEVA FOLFOXIRI/BEVA</td>
</tr>
<tr>
<td>sx</td>
<td></td>
</tr>
</tbody>
</table>

1° line: FOLFOXIRI/BEVA
2° line: FOLFOXIRI/Aflibercept

Cetuximab/panitumumab
Bevacizumab or Aflibercept in second line?

- **Bevacizumab**
  - Giantonio (1° line chemo alone)
  - TML (Beyond progression)
  - FIRE 3 (after EGFR inhibitor)

- **Aflibercept**
  - VELOUR (1° line, chemo alone (70%) or plus BEVA)
VELOUR and TML are different: clinical

<table>
<thead>
<tr>
<th>Study population</th>
<th>VELOUR 1226 patients</th>
<th>TML 819 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early progressor (1L PFS&lt;3 mo)</td>
<td>eligible</td>
<td>Non eligible</td>
</tr>
<tr>
<td>Progression &gt;3 mo after last dose of 1L bevacizumab</td>
<td>eligible</td>
<td>Non eligible</td>
</tr>
<tr>
<td>Patients progressing within 6 mo after adjuvant therapy</td>
<td>Eligible (16%)</td>
<td>Non eligible</td>
</tr>
</tbody>
</table>

VELOUR and TML are different: biological

VELOUR post hoc biomarker analysis
Patients receiving prior bevacizumab treatment express higher plasma VEGF-A and PIGF

This analysis aimed to determine the impact of increased VEGF-A and PIGF levels post-bevacizumab on patient outcomes. OS and PFS analyses were performed based on:
- Prior bevacizumab treatment or baseline growth factor levels
- Then further separated into study treatment groups (afiblercept versus placebo)

VELOUR biomarker population: n = 533/1226 patients with VEGF-A and PIGF data (measured at baseline of the VELUX trial)

Growth factor levels, PFS and OS: Afiblercept versus placebo, prior bev versus no prior bev treatment

<table>
<thead>
<tr>
<th></th>
<th>Mean VEGF-A</th>
<th>Mean PIGF</th>
<th>mPFS, months (95% CI)</th>
<th>mOS, months (95% CI)</th>
<th>Afiblercept vs placebo Difference in OS, months</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>753.1</td>
<td>20.7</td>
<td>3.9 (3.0–4.4)</td>
<td>10.6 (9.1–12.5)</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>Afiblercept</td>
<td>762.6</td>
<td>23.1</td>
<td>7.2 (5.7–8.6)</td>
<td>12.1 (10.0–16.4)</td>
<td></td>
<td>1.5</td>
</tr>
</tbody>
</table>

Treatment algorithm based on molecular and clinical features

MUT

B-RAF

FOLFOXIRI/BEVA

1° line

RAS

FOLFOX/FOLFIRI

FOLFOXIRI/BEVA

dx

dx

2° line

Folﬁri/Aflibercept

?

sx

sx

3° line

Folﬁri/Aflibercept

?
### THIRD-LINE OPTIONS...

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>N. pts</em></td>
<td>505 (wt+mt)</td>
<td>800 (wt+mt)</td>
<td>215 (wt)</td>
<td>119 (wt)</td>
</tr>
<tr>
<td>RR</td>
<td>1% vs 0%</td>
<td>1.6% vs 0.4%</td>
<td>13% vs 0%</td>
<td>17% vs 0%</td>
</tr>
<tr>
<td>PFS</td>
<td>1.9 vs 1.7</td>
<td>2 vs 1.7</td>
<td>3.7 vs 1.9</td>
<td>12.3 vs 7.3 wks</td>
</tr>
<tr>
<td>OS</td>
<td>6.4 vs 5.0</td>
<td>7.1 vs 5.3</td>
<td>9.5 vs 4.8</td>
<td>8.1 vs 7.6 months</td>
</tr>
</tbody>
</table>

**CORRECT**
Regorafenib vs. Placebo

mOS 5.0 vs 6.4 mos  
HR: 0.77

**RECOUERSE**
TAS-102 vs. Placebo

mOS 5.3 vs 7.1 mos  
HR: 0.68

Select the patients!  
Only for patients with PS 0-1  
No liver mets (Rego)  
Starting dose and dose adjustment (Rego)  
Toxicity profile (Rego vs. TAS)

Grothey A et Al, Lancet 2012  
Mayer R et Al, New Eng J Med 2015
Treatment algorithm based on molecular and clinical features

MUT

- B-RAF
  - 1° line: FOLFOXIRI/BEVA
  - 2° line: Folfiri/Aflibercept
  - 3° line: TAS102/Regorafenib

WT

- RAS
  - 1° line: FOLFOX/FOLFIRI
  - 2° line: Folfiri/Aflibercept
  - 3° line: TAS102/Regorafenib

- dx
  - FOLFOX/FOLFIRI BEVA
  - FOLFOXIRI/BEVA

- sx
  - Cetuximab/panitumumab

ESO-ESMO EEBR Masterclass 2019
Step forward in precision medicine in McRC

**HERACLES: trastuzumab + laptinib**

- 27 HER2+ KRAF wt mCRC pts progressed after fluoropyr, oxaliplatin, irinotecan and an anti-EGFR mAb
- Patients given trastuzumab and laptinib (n=27)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Response</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1 (4%)</td>
<td>3</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (4%)</td>
<td>3</td>
</tr>
<tr>
<td>Stable disease &lt;16 weeks</td>
<td>8 (30%)</td>
<td>26</td>
</tr>
<tr>
<td>Stable disease &gt;16 weeks</td>
<td>4 (15%)</td>
<td>24</td>
</tr>
<tr>
<td>Objective response</td>
<td>8 (30%)</td>
<td>26</td>
</tr>
<tr>
<td>Disease control</td>
<td>8 (30%)</td>
<td>26</td>
</tr>
<tr>
<td>Duration of response (weeks)</td>
<td>8 (30%)</td>
<td>26</td>
</tr>
<tr>
<td>Time to response (weeks)</td>
<td>8 (30%)</td>
<td>26</td>
</tr>
</tbody>
</table>

**Characteristics of ALK/ROS/NTRK rearranged mCRC**

- Female: Elderly
- Right colon: Nodal mets
- RAS&RAFI wt: MSI-high

**BEST RESPONSE TO PREVIOUS Anti-EGFR: PROGRESSIVE DISEASE 100% (4/4)**

**MSI and Colorectal Cancer**

- 15-20% of colorectal cancers are MSI+, one third belong to LS due to mutations in MMR genes (MLH1, MSH2, MSH6, PM22)
- The rest are sporadic MSI, mainly due to somatic tumor MLH1 promoter methylation (C region)
- Correlated with tumor BRAF V600E mutation


Immune checkpoint inhibitors (ICI) are increasingly recognized as effective therapeutic agents in the treatment of colorectal cancer (CRC), especially in patients with microsatellite instability-high (MSI-H) tumors. MSI-H CRC is characterized by defects in DNA mismatch repair (MMR), leading to an increased mutation burden and immune dysregulation.

In a pivotal trial, patients with metastatic MSI-H CRC were treated with nivolumab, a programmed cell death protein 1 (PD-1) inhibitor. The trial showed promising results, with an objective response rate of 62% and a disease control rate of 92% in the MMR-deficient group compared to 0% and 16% in the MMR-proficient group.

This study highlights the potential of ICI in patients with MSI-H CRC, offering a new therapeutic option for this subset of patients. Further research is warranted to explore the optimal use of ICI in CRC and to identify biomarkers that can predict response to therapy.
Advanced colorectal cancer: an impressive progress after 30 years of clinical research

This progress was achieved without 2°/3° lines and by considering RAS/BRAF only

5% vs 25%