Systemic treatment in advanced colon cancer

Stefano Cascinu
Department of Medical Oncology
University Vita-Salute; IRCCS-Hospital San Raffaele
Milan, Italy
Stefano Cascinu

Conflict of interest disclosure:

- Consultant or Advisory Board:
  Amgen; Lilly; Bayer; Servier;

- Research grant:
  EISAI

- Honoraria:
  Lilly; Amgen; Bayer; Servier
The treatment of the advanced disease and the improvement in survival
How has been this advancement in the management of advanced disease achieved 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) and the selection of treatments
The patients with advanced colon cancer: a heterogeneous population

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
- Synchronous metastases
- CEA > 100 ng/mL

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

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

The Tower of Babel of liver metastases from colorectal cancer: Are we ready for one language?
Colorectal cancer is the only metastatic tumour where a local treatment may cure, but an “adjuvant” systemic treatment should be offered to most patients.
Adjuvant therapy after metastasectomy

The adjuvant French trial comparing FOLFIRI to SFU/LV in patients with resected colorectal liver metastases

<table>
<thead>
<tr>
<th></th>
<th>LV/SFU (n. 353)</th>
<th>FOLFIRI (n. 353)</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>21.6 months</td>
<td>24.7 months</td>
<td>0.89</td>
<td>0.44</td>
</tr>
<tr>
<td>3 yrs survival</td>
<td>72%</td>
<td>73%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No room for an adjuvant therapy unless .....
No room for an adjuvant therapy unless…..

• Patients did not receive an adjuvant therapy for primary tumor and recurrence is within 12 months from surgery for primary (Stage B)

• Patients received a fluoropyrimidine based therapy. In this case you can think to an oxaliplatin based regimen
Can we select the patients benefiting from a surgical approach even when resectable?
The resectability in terms of biology and not of surgical criteria

Clinical Score for Predicting Recurrence After Hepatic Resection for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Score</th>
<th>1-yr</th>
<th>2-yr</th>
<th>3-yr</th>
<th>4-yr</th>
<th>5-yr</th>
<th>Median (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>93</td>
<td>79</td>
<td>72</td>
<td>60</td>
<td>60</td>
<td>74</td>
</tr>
<tr>
<td>1</td>
<td>91</td>
<td>78</td>
<td>66</td>
<td>54</td>
<td>44</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>89</td>
<td>73</td>
<td>60</td>
<td>51</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>86</td>
<td>67</td>
<td>42</td>
<td>25</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>45</td>
<td>38</td>
<td>29</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>45</td>
<td>27</td>
<td>14</td>
<td>14</td>
<td>22</td>
</tr>
</tbody>
</table>

Each risk factor is one point: node-positive primary, disease-free interval <12 months, >1 tumor, Size >5 cm, CEA >200 ng/ml.

Thee need to identify preoperatively the resectable liver metastases at LOW or HIGH RISK (perioperative treatment)
New criteria?
Clinical: sidedness; Tumor biology?
Treatment: a selection based on molecular profile?

- **FOLFOXIRI/Bevacizumab**

![Graphs showing survival data](image)

- Schirripa et al, Br J Cancer '15
- Teng, Ann Surg Oncol 2012
- Cremolini et al, Eur J Cancer ‘17
**BRAF** mutation is not associated with an increased risk of recurrence in patients undergoing resection of colorectal liver metastases

J.-B. Bachet\(^1\)\(^2\), N. Moreno-Lopez\(^3\), L. Vigano\(^5\), U. Marchese\(^6\), M. Gelli\(^7\), L. Raoux\(^8\), S. Truant\(^10\), C. Laurent\(^12\), A. Herrero\(^13\)\(^14\), B. Le Roy\(^14\)\(^16\), S. Deguelte Lardièr\(^e\)\(^15\), G. Passot\(^10\)\(^16\), V. Hautefeuille\(^17\), C. De La Fouchardière\(^18\), P. Artru\(^19\), T. Ameto\(^11\), J. Y. Mabrut\(^20\), L. Schwarz\(^21\), B. Rousseau\(^22\), C. Lepère\(^3\), R. Coriat\(^4\), A. Brouquet\(^23\)\(^24\), A. Sa Cunha\(^8\)\(^24\) and S. Benoist\(^23\)\(^24\)

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**Fig. 1** Disease-free survival curves for whole population (249 patients) according BRAF status

<table>
<thead>
<tr>
<th>BRAF Status</th>
<th>Time (months)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>wtBRAF</td>
<td></td>
<td>183</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66</td>
</tr>
</tbody>
</table>

**Fig. 2** Overall survival curves for whole population (249 patients) according BRAF status

<table>
<thead>
<tr>
<th>BRAF Status</th>
<th>Time (months)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>wtBRAF</td>
<td></td>
<td>183</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66</td>
</tr>
</tbody>
</table>

**Fig. 3** Overall survival curves for the subgroup of 158 patients who experienced disease recurrence according BRAF status

<table>
<thead>
<tr>
<th>BRAF Status</th>
<th>Time (months)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>wtBRAF</td>
<td></td>
<td>144</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44</td>
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</tbody>
</table>

*wtBRAF, wild-type BRAF; mutBRAF, mutated BRAF*
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><strong>Low Risk</strong></td>
<td><strong>Biologically challenging</strong></td>
<td><strong>Technically challenging</strong></td>
</tr>
</tbody>
</table>
| - Single M+  
  - Size ≤ 5 cm  
  - N0 at primary tumor  
  - Metachronous  
  - CEA ≤ 100 ng/mL | - Multiple metastases  
  - Size > 5 cm  
  - N+ at primary tumor  
  - Synchronous metastases  
  - CEA > 100 ng/mL | - Close to hepatic veins or portal branches  
  - Major hepatectomy required |
| **Surgery** | **Peri-operative Chemotherapy + Surgery** | **Conversion Chemotherapy + Surgery (if sufficient response)** |
| | | **Palliative Chemotherapy** |
| | | **Ultimately Resectable** |
| | | - >70-80% of liver involvement  
  - < 25% remnant after resection  
  - 6 segments involved |
| | | **Never resectable** |
| | | - Unresectable extrahepatic disease |

Bittoni A et al, CROH 2013
THE FOLFOX REGIMEN!
no biological agents

Neoadjuvant (Perioperative) Chemotherapy in Resectable CRC Liver Metastases
EORTC 40983 (EPOC) and New EPOC

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

• 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</th>
<th>GRECCA R²</th>
<th>SYNCHRONOUS³</th>
<th>CLIMAT⁴</th>
<th>NCT02149784⁵</th>
<th>NCT02291744⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>360</td>
<td>290</td>
<td>522</td>
<td>278</td>
<td>480</td>
<td>130</td>
</tr>
<tr>
<td>Regimen</td>
<td>PTR-5FU+Bev Chemo vs 5FU+Bev Chemo</td>
<td>PTR-Chemo vs Chemo+bev</td>
<td>PTR-Chemo vs Chemo</td>
<td>PTR-Chemo vs Chemo</td>
<td>Chemo vs Chemo-5FU+Bev</td>
<td>XELOX vs XELOX-5FU+Bev</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>III</th>
<th>III</th>
<th>III</th>
<th>III</th>
<th>III</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>TFS</td>
</tr>
<tr>
<td>Site</td>
<td>Colorectal</td>
<td>Rectum</td>
<td>Colon</td>
<td>Colon</td>
<td>Colon or rectal</td>
<td>Colon</td>
</tr>
<tr>
<td>Status</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>NA</td>
</tr>
</tbody>
</table>

When it makes sense to consider resection of primary tumour?

• Symptomatic for occlusion, bleeding
• Potentially resectable metastases
• Easily resectable with no extensive liver involvement
Technically challenging liver metastases: The benefit of a tumor shrinkage

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

- **Potentially Resectable**
  - Surgery
  - Peri-operative Chemotherapy + Surgery

- **Unresectable**
  - Ultimately Resectable
    - >70-80% of liver involvement
    - < 25% remnant after resection
    - 6 segments involved
  - Conversion Chemotherapy + Surgery (if sufficient response)

- **Never resectable**
  - Unresectable extrhepatic disease
  - 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>FOLFIRI</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/panitumab</td>
<td>57%</td>
<td>30-38% (LO)</td>
<td>Skin; diarrhea</td>
</tr>
<tr>
<td>FOLFOXIRI/Panitumab</td>
<td>85%</td>
<td>70% (LO)</td>
<td>Skin; diarrhea</td>
</tr>
</tbody>
</table>
Molecular features are crucial points

- RAS WT; BRAF WT
- RAS mut or B-RAF mut

EGFR based regimen
FOLFOXIRI/Beva

But keep in our mind that ....

The more prolonged the Chemo...
The higher the Number of lines...
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 and above all the sequences of 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
ESMO

1st line treatment of mCRC: ESMO consensus guidelines

Assessment of clinical condition of the patient

Fit

Unfit (but may be suitable)

Unfit

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

- MUT
- RAS/BRAF WT
  - B-RAF
  - RAS
  - FOLFOXIRI/BEVA

1° line
The BRAF mutated tumors: poor prognosis and outcome to conventional therapy but not to more aggressive regimens

BRAF mut
HR: 0.908, p=0.74

Van Cutsem J
Clin Oncol ‘11

MT RAS
15.6
19.2
1.25
0.04

MT BRAF
10.5
9.2
0.90
0.76

WT RAS
26.0
20.2
0.78
0.04

WT RAS and BRAF
28.3
20.9
0.74
0.02

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

1° line

B-RAF

RAS

MUT

FOLFOXIRI/BEVA

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

- MUT
  - B-RAF
  - RAS
- WT BRAF/RAS
  - ?

1° line
- FOLFOXIRI/BEVA
- FOLFOX/FOLFIRI BEVA
- FOLFOXIRI/BEVA

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An old question in RAS/BRAF wt: The best targeted agents to be used in first line
An old, debated question in RAS/BRAF wt: The best targeted agents to be used in first line

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


Overall survival

28.7 months

Bevacizumab + CT (FOLFIRI) (n=295)

Cetuximab + CT (FOLFIRI) (n=297)

Δ = 3.7 months

HR=0.77
p=0.017

MONTHS SINCE START OF TREATMENT

25.0 months

JOURNAL OF CLINICAL ONCOLOGY

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

Luc G. Schwemmberger, Fernando Ayala, Mario Martucci, Gianmario Federico, Jean-Luc Coyer, J. Aukrust Philip, Ilia Yu, Kelly J. Oliver, and William T. Co
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?
Another question: Does primary tumor sidedness matter?

<table>
<thead>
<tr>
<th>Category</th>
<th>No. response</th>
<th>No. entered</th>
<th>Odds ratio</th>
<th>OR interaction [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT ± bevacizumab</td>
<td>CT + anti-EGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIRE3 - Left</td>
<td>92/149</td>
<td>108/157</td>
<td>0.81</td>
<td>[0.31–2.13]; P = 0.67</td>
</tr>
<tr>
<td>FIRE3 - Right</td>
<td>25/50</td>
<td>20/38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB80405 - Left</td>
<td>88/152</td>
<td>120/173</td>
<td>0.67</td>
<td>[0.34–1.35]; P = 0.26</td>
</tr>
<tr>
<td>CALGB80405 - Right</td>
<td>31/78</td>
<td>30/71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEAK - Left</td>
<td>31/54</td>
<td>34/53</td>
<td>1.32</td>
<td>[0.36–4.77]; P = 0.67</td>
</tr>
<tr>
<td>PEAK - Right</td>
<td>7/14</td>
<td>14/22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRYSTAL - Left</td>
<td>56/138</td>
<td>103/142</td>
<td>0.36</td>
<td>[0.13–1.04]; P = 0.06</td>
</tr>
<tr>
<td>CRYSTAL - Right</td>
<td>17/51</td>
<td>14/33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRIME - Left</td>
<td>82/156</td>
<td>114/168</td>
<td>0.72</td>
<td>[0.29–1.74]; P = 0.46</td>
</tr>
<tr>
<td>PRIME - Right</td>
<td>16/46</td>
<td>16/38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20050181 - Left</td>
<td>19/144</td>
<td>73/147</td>
<td>0.88</td>
<td>[0.09–8.84]; P = 0.91</td>
</tr>
<tr>
<td>20050181 - Right</td>
<td>1/38</td>
<td>4/30</td>
<td>(0.69</td>
<td>[0.46–1.04]; P = 0.07</td>
</tr>
<tr>
<td><strong>Total - Left</strong></td>
<td><strong>368/793</strong></td>
<td><strong>552/840</strong></td>
<td><strong>2.12</strong></td>
<td><strong>[1.77–2.55]; P &lt; 0.001</strong></td>
</tr>
<tr>
<td><strong>Total - Right</strong></td>
<td><strong>97/277</strong></td>
<td><strong>98/232</strong></td>
<td><strong>1.47</strong></td>
<td><strong>[0.94–2.29]; P = 0.089</strong></td>
</tr>
</tbody>
</table>

Between HR interaction heterogeneity: P = 0.77

CT ± bevacizumab better | CT + anti-EGFR better
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>Left-sided</td>
<td>ESMO¹</td>
<td>NCCN²</td>
<td>Axel Grothey³</td>
</tr>
<tr>
<td>ESMO¹</td>
<td>NCCN²</td>
<td>EGFR mAbs are preferred, bevacizumab can be used in select patients in 1st line</td>
<td>EGFR mAbs are preferred after discussion with patient</td>
</tr>
<tr>
<td>Right-sided</td>
<td>ESMO¹</td>
<td>NCCN²</td>
<td>Axel Grothey³</td>
</tr>
<tr>
<td>ESMO¹</td>
<td>NCCN²</td>
<td>No EGFR mAbs in 1st line (if response is goal, consider triplet), but allow EGFR mAbs in later line</td>
<td>No EGFR mAbs in 1st line, 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
    - dx
      - WT
        - BRAF/RAS
      - sx
    - FOLFOXIRI/BEVA
      - FOLFOX/FOLFIRI (!)
        - BEVA
          - FOLFOXIRI/BEVA
          - FOLFOX/FOLFIRI BEVA
          - Cetuximab/pa nitumumab/ch emotherapy

A critical point: how long have we treat a patient in first line? Or in other words, is maintenance treatment worthwhile?
Maintenance with bevacizumab:

Maintenance with panitumumab:
Elderly patients or with a PS2

Accrual completed!

Panda Study
Randomized phase 2 study of first-line FOLFOX plus panitumumab versus 5FU plus pan in elderly RAS and BRAF wild-type metastatic colorectal cancer patients

G.O.N.O
Gruppo Oncologico del Nord Ovest

Cunningham D. et al, Lancet Oncol. 2013
PS 2 due to disease: what to do

• No monotherapy with fluoropyrimidines (Focus, Optimox)

• Polichemotherapy: similar benefit to PS0-1 but increased risk of several toxicities (Sargent, JCO 2009)

• No combination with biologicals
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 2°-line treatment decisions? ESMO guidelines

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment goal</th>
<th>Molecular profile</th>
<th>RAS wt</th>
<th>RAS mt</th>
<th>BRAF mt</th>
<th>Disease control (control of progression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line</td>
<td>Cytoreduction (tumour shrinkage)</td>
<td>Preferred choice (s)</td>
<td>CT doublet + EGFR antibody(^{cd})</td>
<td>CT doublet + bevacizumab</td>
<td>FOLFOXIRI + bevacizumab</td>
<td>CT doublet + bevacizumab or CT doublet + EGFR antibody</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second choice</td>
<td>FOLFOXIRI + bevacizumab</td>
<td>FOLFOXIRI + bevacizumab</td>
<td>CT doublet + bevacizumab</td>
<td>FP + bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third choice</td>
<td>CT doublet + bevacizumab</td>
<td>FOLFOXIRI</td>
<td>FOLFOXIRI</td>
<td>FP + bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance</td>
<td>FP + bevacizumab</td>
<td>FP + bevacizumab</td>
<td>FP + bevacizumab</td>
<td>FP + bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second choice</td>
<td>Pause</td>
<td>Pause</td>
<td>Pause</td>
<td>Pause</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preferred choice (s)</td>
<td>CT doublet + EGFR antibody(^{d})</td>
<td>CT doublet + bevacizumab</td>
<td>CT doublet + bevacizumab</td>
<td>CT doublet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second choice</td>
<td>FOLFOXIRI + afibercept/ramucirumab</td>
<td>FOLFOXIRI + afibercept/ramucirumab</td>
<td>FOLFOXIRI + afibercept/ramucirumab</td>
<td>FOLFOXIRI + afibercept/ramucirumab</td>
</tr>
</tbody>
</table>

Treatment algorithm based on molecular and clinical features

MUT

B-RAF

1° line

FOLFOXIRI/BEVA

FOLFOX/FOLFIRI/BEVA

2° line

FOLFIRI/AFLIBERCEPT

RAS

dx

WT

sx

FOLFOX/FOLFIRI/BEVA

FOLFOXIRI/BEVA

panitumumab

Cetuximab/panitumumab

?
## BRAF population in the VELOUR trial

<table>
<thead>
<tr>
<th>BRAF population</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>BRAF wt</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>HR (95%CI)</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>BRAF mutant</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>HR (95%CI)</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>Interaction test</td>
<td></td>
<td>0.08</td>
<td>0.29</td>
<td>0.98</td>
</tr>
</tbody>
</table>
The treatment for B-RAF mutant tumours: no more chemotherapy? The BEACON trial

Targeted triplet in BRAF mut? BEACON trial

Phase III randomized trial

665 patients with BRAF V600 mutations progressing after 1-2°line therapy Kopetz WGI 2019

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MOS</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>224 encorafenib; binimetinib; cetuximab</td>
<td>9</td>
<td>26%</td>
</tr>
<tr>
<td>R 220 encorafenib; cetuximab</td>
<td>8.4</td>
<td>-</td>
</tr>
<tr>
<td>221 FOLFIRI/cetuximab</td>
<td>5.4</td>
<td>2%</td>
</tr>
</tbody>
</table>
Treatment algorithm based on molecular and clinical features

MUT

B-RAF

RAS

WT

dx

sx

1° line

FOLFOXIRI/BEVA

FOLFOX/FOLFIRI BEVA

FOLFOX/FOLFIRI BEVA

FOLFOXIRI/BEVA

Cetuximab/pa nitumumab

2° line

FOLFIRI/Afl ibercept

?
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 beva</td>
<td>eligible</td>
<td>Non eligible</td>
</tr>
<tr>
<td>Patients progressing within 6mo after adjuvant therapy</td>
<td>Eligible (10%)</td>
<td>Non eligible</td>
</tr>
</tbody>
</table>

**VELOUR and TML are different: biological**

**Why may afilircept be better than bevacizumab in previously bevacizumab-treated patients? A preclinical rationale**

**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 (afilircept versus placebo).

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

<table>
<thead>
<tr>
<th></th>
<th>Mean VEGF-A, pg/mL</th>
<th>Mean PIGF, pg/mL</th>
<th>mPFS, months (95% CI)</th>
<th>mOS, months (95% CI)</th>
<th>Afilircept vs placebo Difference in OS, months (HR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 79)</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>0.84 (0.59–1.2)</td>
</tr>
<tr>
<td>Afilircept (n = 90)</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>
</tr>
<tr>
<td>Placebo (n = 186)</td>
<td>165.4</td>
<td>11.4</td>
<td>4.9 (4.2–5.7)</td>
<td>11.4 (9.9–12.7)</td>
<td></td>
</tr>
<tr>
<td>Afilircept (n = 198)</td>
<td>148.9</td>
<td>12.0</td>
<td>6.8 (5.0–7.5)</td>
<td>12.9 (11.9–15.7)</td>
<td></td>
</tr>
</tbody>
</table>
Treatment algorithm based on molecular and clinical features

MUT

B-RAF

FOLFOXIRI/BEVA

1° line

RAS

FOLFOX/FOLFIRI
BEVA

2° line

dx

FOLFOX/FOLFIRI
BEVA

3° line

WT

sx

FOLFOXIRI/BEVA

Folfiri/Aflibercept

Folfiri/Aflibercept/Beva

Folfiri/FolfoxAf
libercept/Beva

Cetuximab/panitumumab

Panitumumab
## THIRD-LINE OPTIONS...

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regorafenib \textit{Lancet 2013}</th>
<th>TAS 102 \textit{NEJM 2015}</th>
<th>Cetuximab \textit{NEJM 2008}</th>
<th>Pani \textit{JCO 2008}</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{N. pts}</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

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)

RECOVERY
TAS-102 vs. Placebo
mOS 5.3 vs 7.1 mos
HR: 0.68

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

MUT

1° line
- B-RAF
  - FOLFOXIRI/BEVA

2° line
- RAS
  - FOLFOX/FOLFIRI/BEVA
  - Cetuximab/panitumumab
- dx
  - FOLFOX/FOLFIRI/BEVA

3° line
- MUT
  - Folfin/Aflibercept
  - Bevaci/Bev/Bev/Pan
  - TAS102/Regorafenib
  - TAS102/Regorafenib
Another option: the rechallenge
A close future in colorectal cancer
Precision medicine
Immunotherapy
Step forward in precision medicine in McRC

From negative prediction

No anti-EGFRs!

RAS wild-type
50%
RAS mutant
50%

To target philosophy

ALK/ROS/NTRK1,2,3 fusions

HER-2 (5%)

RAS/BRaf wild-type
10%

RET fusions

RAS-BRAF mutation

MSI 5%

FGFR amplification

50%

Cremolini and Falcone, 2017

HERACLES: trastuzumab + lapatinib

27 HER-2 +, KRAS wt mCRC pts progressed after fluoropyrimidine, oxaliplatin, irinotecan and an anti-EGFR mAb

Complete response
1 (4%, 1 to 11)

Partial response
7 (26%, 5 to 42)

Stable disease >16 weeks
8 (30%, 13 to 47)

Stable disease <16 weeks
4 (15%, 1 to 27)

Objective response
8 (30%, 13 to 47)

Disease control
16 (59%, 39 to 76)

Duration of response (weeks)
8 (2.8 to 4.2)

Time to response (weeks)
8 (3 to 16)

Sartore Blanchi et al, Lancet Oncology, ’16

Characteristics of ALK/ROS/NTRK rearranged mCRC

Female Elderly
Right colon Nodal mets
RAS&BRaf 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, PM2)
The rest are sporadic MSI, mainly due to somatic tumor MLH1 promoter methylation (C region)
Correlated with tumor BRAF V600E mutation

Pietrantoni & Cremolini, JNCI ’17
Going to the superRARE!

Rolfo et al, Expert Opin Investig Drugs 2015

Madison et al, ESMO 2018, abstr 3509

NGS testing on 21,000 CRC pts including fusion, MSI

<table>
<thead>
<tr>
<th>Kinase</th>
<th>N cases</th>
<th>% MSI-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>FGFR2</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>NTRK1</td>
<td>26</td>
<td>85</td>
</tr>
<tr>
<td>NTRK3</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>RET</td>
<td>27</td>
<td>50</td>
</tr>
</tbody>
</table>

Overall prevalence:
~0.4%
Number needed to screen 250

Prevalence in MSI-H:
~10%
Number needed to screen 10
Immunotherapy in colorectal cancer: the MSI tumours

Table: Objective response, best overall response, and disease control per investigator and blinded independent central review assessments.

<table>
<thead>
<tr>
<th>MMR-deficient CRC</th>
<th>MMR-proficient CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Objective Response Rate</td>
</tr>
<tr>
<td>13</td>
<td>62%</td>
</tr>
<tr>
<td>25</td>
<td>0%</td>
</tr>
</tbody>
</table>

Overman MJ et al, Lancet Oncol 2017
REGONIVO Trial: Fase I trial in MSS gastric and colon cancer patients

Dose escalation cohort: "3+3" design

- Regorafenib Level 1: 80 mg/day 21 on 7 days off + Nivolumab 3 mg/kg q2w
  - N = 3~6
- Regorafenib Level 2: 120 mg/day 21 on 7 days off + Nivolumab 3 mg/kg q2w
- Regorafenib Level 3: 160 mg/day 21 on 7 days off + Nivolumab 3 mg/kg q2w
  - N = 3~6

Expansion cohort

- Colorectal cancer
- Gastric cancer
- Total 36 cases

Primary objective: dose-limiting toxicity (DLT) during cycle one to investigate the maximum tolerated dose (MTD) and recommended dose (RD)

Secondary objective: objective response rate (ORR), progression-free survival (PFS), overall survival (OS), disease control rate (DCR)

Change from baseline (%)

- ORR 40% (95% CI: 26-55)
- DCR 88% (95% CI: 76-96)
- ORR 45% in Rego 80mg, 36% in 120mg, and 33% in 160mg
Define the best treatment strategy for each patient

• Which patient is in front of us (Fit/not Fit, young/elderly)

• Which kind of disease the patient has (resectable/not resectable, RAS/BRAF mut/wt)

• Which toxicity the patient may accept
Probably if we do so, these improvements in survival may be achievable in our daily clinical practice.