Treatment strategies for advanced or metastatic colorectal cancer

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Shanghai, China
1. The first-line chemotherapy for advanced colorectal cancer

2. New options of targeted-drugs

3. The second-line and cross-line treatment for advanced colorectal cancer
## Phase III clinical trials of first-line mCRC using Irinotecan combined with 5-FU/LV

<table>
<thead>
<tr>
<th>Author</th>
<th>Protocol</th>
<th>RR (%)</th>
<th>PFS (mos)</th>
<th>OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltz,</td>
<td>FU/ LV bolus (Mayo)</td>
<td>21</td>
<td>4.3</td>
<td>12.6</td>
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<tr>
<td>NEJM 9/2000</td>
<td>FU/ LV bolus + Irinotecan (IFL)</td>
<td>39</td>
<td>7.0</td>
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<tr>
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<td>p-value</td>
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<td>0.004</td>
<td>0.04</td>
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<tr>
<td>Douillard,</td>
<td>FU/ LV inf.</td>
<td>31</td>
<td>4.4</td>
<td>14.1</td>
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<tr>
<td>Lancet 3/2000</td>
<td>FU/ LV inf. + Irinotecan</td>
<td>49</td>
<td>6.7</td>
<td>17.4</td>
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<td>16.9</td>
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<td>ASCO 2003</td>
<td>FU/ LV inf. + Irinotecan</td>
<td>54.2</td>
<td>8.5</td>
<td>20.1</td>
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<tr>
<td>#430</td>
<td>p-value</td>
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<td>0.0001</td>
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## Phase III clinical trials of first-line mCRC using Oxaliplatin combined with 5-FU/LV

<table>
<thead>
<tr>
<th>Author</th>
<th>Protocol</th>
<th>RR (%)</th>
<th>PFS (mos)</th>
<th>OS (mos)</th>
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<tbody>
<tr>
<td>Giacchetti,</td>
<td>FU/LV inf.</td>
<td>16</td>
<td>6.1</td>
<td>19.9</td>
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<tr>
<td>JCO 1/ 2000</td>
<td>FU/LV inf. + Oxaliplatin</td>
<td>53</td>
<td>8.7</td>
<td>19.4</td>
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<tr>
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<td>0.048</td>
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<tr>
<td>De Gramont,</td>
<td>FU/LV inf.</td>
<td>22.3</td>
<td>6.2</td>
<td>14.7</td>
</tr>
<tr>
<td>JCO 8/ 2000</td>
<td>FU/LV inf. + Oxalipl. FOLFOX4</td>
<td>50.7</td>
<td>9.0</td>
<td>16.2</td>
</tr>
<tr>
<td>#420</td>
<td>p-value</td>
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<td>&lt;0.0001</td>
<td>n.s.</td>
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<tr>
<td>Grothey,</td>
<td>FU/ LV Bolus (Mayo)</td>
<td>22.6</td>
<td>5.3</td>
<td>16.1</td>
</tr>
<tr>
<td>ASCO 2002</td>
<td>FU/ LV inf. + Oxaliplatin</td>
<td>49.1</td>
<td>7.8</td>
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<td>n.s.</td>
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</table>
Tournigand Study

Arm A

Previously untreated MCRC

FOLFIRI → PD → FOLFOX-6 → PD

Arm B

FOLFOX-6 → PD → FOLFIRI → PD

PD = progressive disease.

Overall Survival

Survival time

OS estimate

Logrank

p = 0.9

FOLFIRI / FOLFOX

FOLFOX / FOLFIRI
Concept of “All-3-Drugs” - Update 2005
11 Phase III Trials, 5768 Patients

Multivariate analysis:
Effect on OS $P$
First-line doublet 0.69
All 3 drugs 0.005

Median OS (mo)
Patients with 3 drugs (%)

First-Line Therapy
- Infusional 5-FU/LV + irinotecan
- Infusional 5-FU/LV + oxaliplatin
- Bolus 5-FU/LV + irinotecan
- Bolus 5-FU/LV + oxaliplatin
- LV5FU2

OS (mos) = 13.2 + (%3drugs x 0.1), $R^2 = 0.85$

Grothey & Sargent, JCO 2005
Summary:

1. Patients appropriate for intensive therapy, FOLFIRI, FOLFOX, XELOX all can be chosen as the first-line therapy.

2. Patients not appropriate for intensive therapy, 5-FU/LV or Capecitabine monotherapy can be chosen as the first-line therapy.
In this case:

- So far:
  - 4 mos. FOLFOX/Bev $\rightarrow$ 9 mos. Cape/Bev (= 13 in total)
  - 7 mos. FOLFIRI/Aflibercept (with some interruptions), stable disease
  - 4 mos. Panitumumab single agent $\rightarrow$ some response, then progression
- What now?
  - FOLFOX (Re-Induction) $\rightarrow$ Regorafenib ?
  - Regorafenib $\rightarrow$ FOLFOX (Re-Induction)
  - How to integrate TAS 102 ?
To patients not appropriate for intensive therapy, infusional 5-FU is still one of the standard options.

Treatment of metastatic disease

Maintenance treatment

- Patients receiving FOLFOX or CAPOX as induction therapy should be allocated to maintenance therapy after 6–8 cycles.
- Patients receiving FOLFIRI as induction should continue for (at least) as long as tumour shrinkage continues/disease stabilisation is maintained.
- In the case of patients receiving induction therapy with single-agent 5-FU/capecitabine or capecitabine plus bevacizumab induction therapy should be maintained until progression.
- Optimal maintenance treatment after a bevacizumab-containing induction is a combination of a fluoropyrimidine plus bevacizumab. Bevacizumab monotherapy as maintenance is not recommended.
- Individualisation and discussion with the patient is essential.
- Induction therapy should be re-introduced throughout the whole treatment strategy.
Targeted-drug therapy for advanced colorectal cancer

- Anti-angiogenic monoclonal anti-body:
  - Bevacizumab
  - Afibercept

- Epidermal growth factor receptor anti-body:
  - Cetuximab
  - Panitumumab
  - Regorafenib
What is the optimal 1st line therapy? Evidence from head-to-head trials

**FIRE-3**
- Patients with untreated KRAS (exon 2) wt mCRC, N=592
- Cetuximab + FOLFIRI
- Bevacizumab + FOLFIRI

**CALGB 80405**
- Patients with untreated KRAS (exon 2) wt mCRC, N≈1200 (after trial modification)
- Cetuximab + FOLFOX/FOLFIRI
- Bevacizumab + FOLFOX/FOLFIRI
- Bevacizumab + cetuximab + FOLFOX/FOLFIRI
  - *Arm closed to accrual as of 09/10/2009*

**PEAK**
- Patients with untreated KRAS (exon 2) wt mCRC, N=285
- Panitumumab + mFOLFOX6
- Bevacizumab + mFOLFOX6

IST, investigator-sponsored trial
FIRE-3: Greater selection of patients further improves the benefit with cetuximab

**KRAS exon 2 wt**

- **Cetuximab + FOLFIRI (n=297)**
- **Bevacizumab + FOLFIRI (n=295)**

**Δ = 3.7 months**

<table>
<thead>
<tr>
<th>OS estimate</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>0.75</td>
<td>12</td>
</tr>
<tr>
<td>0.50</td>
<td>24</td>
</tr>
<tr>
<td>0.25</td>
<td>36</td>
</tr>
<tr>
<td>0.0</td>
<td>48</td>
</tr>
<tr>
<td>0.0</td>
<td>60</td>
</tr>
<tr>
<td>0.0</td>
<td>72</td>
</tr>
</tbody>
</table>

HR 0.77 (95% CI 0.62–0.96)  p=0.017

**RAS wt**

- **Cetuximab + FOLFIRI (n=199)**
- **Bevacizumab + FOLFIRI (n=201)**

**Δ = 8.1 months**

<table>
<thead>
<tr>
<th>OS estimate</th>
<th>Months</th>
</tr>
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<tbody>
<tr>
<td>1.0</td>
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<td>60</td>
</tr>
<tr>
<td>0.0</td>
<td>72</td>
</tr>
</tbody>
</table>

HR 0.697 (95% CI 0.54–0.90)  p=0.0059

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- Overall survival (OS) data are based on an event rate of 59%.
- The FIRE-3 study did not meet its primary endpoint of significantly improving overall response rate (ORR) in patients with KRAS (exon 2) wt mCRC based on investigators' read.
- The study design, crossover treatment in 2nd line and other study attributes are needed to better understand the data.
- The study was financially supported by Merck Serono GmbH.
- Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown.

<table>
<thead>
<tr>
<th>KRAS exon 2 wt (ITT), n</th>
<th>Cetuximab + FOLFIRI</th>
<th>Bevacizumab + FOLFIRI</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>62.0 (56.2–67.5)</td>
<td>58.0 (52.1–63.7)</td>
<td>1.18 (0.85–1.64)</td>
<td>0.183†</td>
</tr>
<tr>
<td>RAS wt*, n</td>
<td>342</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>65.3 (58.3–51.6)</td>
<td>58.7 (51.6–65.6)</td>
<td>1.33 (0.88–1.99)</td>
<td>0.18‡</td>
</tr>
</tbody>
</table>

*Including KRAS exon 2, 3, 4 and NRAS exon 2, 3, 4; †One-sided Fisher’s exact test; ‡two-sided Fisher’s exact test
PEAK study: Overall survival
Panitumumab vs. Bevacizumab in RAS wt mCRC:
WT RAS (exon 2,3,4 KRAS/NRAS)

<table>
<thead>
<tr>
<th>Event</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFOX6 +</td>
<td></td>
</tr>
<tr>
<td>Panitumumab + (n=88)</td>
<td>30 (34) 41.3 (28.8–41.3)</td>
</tr>
<tr>
<td>Bevacizumab + (n=82)</td>
<td>40 (49) 28.9 (23.9–31.3)</td>
</tr>
</tbody>
</table>

HR*=0.63 (95% CI: 0.39–1.02)
p=0.058

Schwartzberg L, et al. JCO 2014
CALGB/SWOG 80405 Study: Overall Survival By Arm

(All RAS Wild Type Patients)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Bev</td>
<td>256 (178)</td>
<td>31.2 (26.9-34.3)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>Chemo + Cetux</td>
<td>270 (177)</td>
<td>32.0 (27.6-38.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# At Risk  
256 199 147 77 35 16 5 2  
270 205 164 88 41 24 7 1  

Lenz et al. ESMO 2014
Treatment of metastatic disease

Fit patients with „disease control“ as goal

- The unanimous recommendation was that they should receive chemotherapy (single-agent/doublet) plus bevacizumab first-line, with EGFR antibody therapy as an option for patients with RAS wild-type disease.
- Patients should be re-evaluated every 2–3 months. Where there is evidence of good disease control, patients should continue on therapy and if after two re-evaluations, active maintenance should be preferrably considered.

Treatment of metastatic disease

Fit patients with cytoreduction or shrinkage as a goal

- For potentially resectable patients with RAS wild-type tumours, a cytotoxic doublet plus an EGFR antibody should be the treatment of choice and those with RAS mutant tumours should receive a cytotoxic triplet ± bevacizumab or cytotoxic doublet plus bevacizumab are the preferred options.
- If, after the first re-evaluation at 2 months, there is evidence of tumour shrinkage, patients should be recommended for potentially curative surgery with a view to eliminating all evidence of disease (R0 resection and/or ablative strategy).
- If no response is evident at first evaluation, it is suggested that the cytotoxic doublet is changed in order to maximise the chance of resection.
Summary:

1 Cetuximab combined with chemotherapy can improve ORR and prolong OS in first-line treatment for the RAS wide type patients.

2 Bevacizumab combined with chemotherapy can prolong PFS in first-line treatment.
## VEGF Inhibition in 2\textsuperscript{nd} or later line therapy

<table>
<thead>
<tr>
<th>VEGF inhibitor</th>
<th>2\textsuperscript{nd} line VEGF</th>
<th>„Last“ line multi VEGF TKI</th>
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</thead>
<tbody>
<tr>
<td>Bev in 1\textsuperscript{st} line</td>
<td>Bev in 1\textsuperscript{st} line</td>
<td>Bev in 1\textsuperscript{st} line</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>FOLFOX</td>
<td>FOLFOX</td>
</tr>
<tr>
<td>FOLFIRI or FOLFOX</td>
<td>FOLFIRI</td>
<td>FOLFIRI</td>
</tr>
<tr>
<td>All pts.</td>
<td>All pts.</td>
<td>All pts.</td>
</tr>
<tr>
<td>no pts</td>
<td>yes / no</td>
<td>(+ EGFR if KRASwt)</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>bevacizumab</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td>afibriccept</td>
<td>afibriccept</td>
<td>regorafenib</td>
</tr>
<tr>
<td>11.2 v 9.8 mo HR 0.81 p=0.0062</td>
<td>12.9 v 10.8 mo HR 0.75 p=0.0011</td>
<td>13.5 v 12.1 mo HR 0.82 p=0.003</td>
</tr>
<tr>
<td>11.7 vs. 13.3 mo HR 0.84 P=0.022</td>
<td>6.4 vs. 5.0 mo HR 0.77 P=0.0052</td>
<td></td>
</tr>
</tbody>
</table>
TML 18147 Study

Unstratified\(^a\) HR: 0.81 (95% CI: 0.69–0.94)  
\(p=0.0062\) (log-rank test)

Stratified\(^b\) HR: 0.83 (95% CI: 0.71–0.97)  
\(p=0.0211\) (log-rank test)

Overall survival composite from 1\(^{st}\) and 2\(^{nd}\) line treatment

22.5 - 9.8 = 12.7 mo
1\(^{st}\) line (CTx+Bev)

23.9 – 11.2 = 12.7 mo
2\(^{nd}\) line (CTx ± Bev)

9.8 mo

22.5 mo
Δ 1.4 mo

23.9 mo
VELOUR Study

Metastatic Colorectal Cancer

Stratification factors:
- ECOG PS (0 vs 1 vs 2)
- Prior bevacizumab (Y/N)

Randomize 1:1

600 patients

Aflibercept 4 mg/kg IV, day 1 + FOLFIRI q2 weeks

Placebo IV, day 1 + FOLFIRI q2 weeks

Disease Progression

Death

DMC review every 6 months

Primary Endpoint: Overall Survival
Overall Survival - ITT Population

Symbol=Censor
Placebo/FOLFIRI  ~ Median = 12.06 months
Aflibercept/FOLFIRI  ~ Median = 13.50 months

Stratified HR=0.817 [95.34%CI, 0.713-0.937]
Log-rank p = 0.0032

Cut-off date = February 7, 2011; Median follow-up = 22.28 months
Summary:

1. VEGF antibodies show OS advantage in second-line treatment.

2. TML 18147 show that Bevacizumab can be used continuously after first-line treatment by Bevacizumab.

3. Afibercept prolong OS in second-line treatment even in patients exposed to Beva.
In this patient case:

- So far:
  - 4 mos. FOLFOX/Bev → 9 mos. Cape/Bev (= 13 in total)
  - 7 mos. FOLFIRI/Aflibercept (with some interruptions), stable disease
  - 4 mos. Panitumumab single agent → some response, then progression

- What now?
  - FOLFOX (Re-Induction) → Regorafenib?
  - Regorafenib → FOLFOX (Re-Induction)
  - How to integrate TAS 102?

**Afiblerecept is an appropriate choice in second-line treatment.**

Regorafenib shows OS advantage in CONCUR study.
CONCUR: Study Design

- **Primary Endpoint**: OS
- **Secondary Endpoints**: PFS, ORR, DCR
- **Stratification factor**:
  - Metastasis: Single vs. Multiple organs
  - Since mCRC diagnosis: ≥ 18 vs. < 18 mo
- **Analysis of sub groups in the treatment plan according to the past targeted therapy (Anti-EGFR, Anti-VEGF)**

**R**

**Second-line mCRC**

N=204

**Disease Progression**

**Regorafenib**

160 mg/d

1 week stop after 3 weeks’ medicine

(4 weeks one cycle)

n=136

**Placebo**

n=68

All patients receive the best supportive care

Assessment every 8 weeks during treatment (CT/MRI)
CONCUR: Primary Endpoint: OS

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>n</td>
<td>136</td>
<td>68</td>
</tr>
<tr>
<td>Events(%)</td>
<td>95 (69.9)</td>
<td>60 (88.2)</td>
</tr>
<tr>
<td>Median OS</td>
<td>8.8 months</td>
<td>6.3 months</td>
</tr>
<tr>
<td>HR(95%CI)</td>
<td>0.55 (0.40-0.77)</td>
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<tr>
<td>p</td>
<td>0.0002</td>
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</table>

Time (Days)
Treatment of metastatic disease

Third and further line therapy

- Regorafenib is recommended in patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with anti-EGFR antibodies
  - Regorafenib is superior to placebo in terms of overall survival, although there are safety / toxicity concerns in frail patients.
- TAS 102 is a (potential) new option for patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with anti-EGFR antibodies
Thank you!