MÁS ALLA DE LA PRIMERA LÍNEA: SECUENCIA DE TRATAMIENTO

Dra. Ruth Vera
Complejo Hospitalario de Navarra

21 junio 2017. Hospital Universitario Miguel Servet. Zaragoza
22 - 24 junio 2017. Hotel Villa de Sallent. Formigal
“GOALS”

• Prolongation of survival
• Cure
• Improving tumour-related symptoms
• Stopping tumour progression
• And/or Quality of life
CONTINUUM OF CARE

Improvement in OS and PFS over time – or: “There is a life after 1st line”
## TREATMENT DECISIONS

<table>
<thead>
<tr>
<th>1st line</th>
<th>2nd and further line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment goal</td>
<td>PRETREATMENT</td>
</tr>
<tr>
<td>Disease-related factors</td>
<td>SEQUENCE ?</td>
</tr>
<tr>
<td>Patient-related factors</td>
<td>Disease-related factors</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Patient-related factors</td>
</tr>
<tr>
<td>Anticipated toxicity</td>
<td>Treatment goal</td>
</tr>
<tr>
<td></td>
<td>Biomarkers</td>
</tr>
</tbody>
</table>
“Backbone of first Chemotherapy”

- Fluoropiridin-based chemotherapy:
  - **Oxaliplatin**
  - **Irinotecan**

  FOLFIRI → FOLFOX
  FOLFOX → FOLFIRI

- Similar activity
- Both partners for biological agents
- Different toxicity profile

Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

E. Van Cutsem¹, A. Cervantes², B. Nordlinger³ & D. Arnold⁴, on behalf of the ESMO Guidelines Working Group

1. Cytotoxic doublet¹ + bevacizumab
2. Cytotoxic doublet¹ + bevacizumab
3. Cytotoxic doublet¹ + anti-EGFR antibody²

A: Scenario 1
B: Scenario 2
C: Scenario 3

1st line
Cytotoxic doublet¹ + bevacizumab
Cytotoxic doublet¹ + bevacizumab
Cytotoxic doublet¹ + anti-EGFR antibody²

2nd line
Cytotoxic doublet¹ + bevacizumab or afiblercept³
Cytotoxic doublet¹ + anti-EGFR antibody²
Cytotoxic doublet¹ + bevacizumab or afiblercept

3rd line
Irinotecan or FOLFIRI + anti-EGFR antibody²
Regorafenib
Regorafenib

4th line
Regorafenib

¹cytotoxic doublets: fluoropyrimidine + oxaliplatin or irinotecan; ²Ras wild type; ³afiblercept only in combination with FOLFIRI
BEST SEQUENCE?

• No data of sequence trials ... but

• 2nd Line trials
  – EPIC, 181, TML, VELOUR, RAISE

• 1st Line trials (analyzing 2L)
  – FIRE-3, PEAK, CALGB
Anti-Angiogenic treatment  ➔ Anti-Angiogenic

A: Scenario 1
- Cytotoxic doublet\(^1\) + bevacizumab
  - Cytotoxic doublet\(^1\) + bevacizumab or aflibercept\(^3\)
    - Irinotecan or FOLFIRI + anti-EGFR antibody\(^2\)
      - Regorafenib

B: Scenario 2
- Cytotoxic doublet\(^1\) + bevacizumab
  - Cytotoxic doublet\(^1\) + anti-EGFR antibody\(^2\)
    - Regorafenib

C: Scenario 3
- Cytotoxic doublet\(^1\) + anti-EGFR antibody\(^2\)
  - Cytotoxic doublet\(^1\) + bevacizumab or aflibercept
    - Regorafenib

\(^1\) cytotoxic doublets: fluoropyrimidine + oxaliplatin or irinotecan; \(^2\) Ras wild type; \(^3\) aflibercept only in combination with FOLFIRI
ML18147 study design (phase III)

- **Primary endpoint**
  - Overall survival (OS) from randomisation

- **Secondary endpoints included**
  - Progression-free survival (PFS)
  - Best overall response rate
  - Safety

- **Stratification factors**
  - First-line CT (oxaliplatin-based, irinotecan-based)
  - First-line PFS (≤9 months, >9 months)
  - Time from last BEV dose (≤42 days, >42 days)
  - ECOG PS at baseline (0/1, 2)

Study conducted in 220 centres in Europe and Saudi Arabia
OS: TML 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)

Median follow-up: CT, 9.6 months (range 0–45.5); BEV + CT, 11.1 months (range 0.3–44.0)
BEBYP study design (phase II)

- Study conducted in 19 Italian centers
- Supported by AIFA


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**Progression-Free Survival (PFS)**

- **Chemotherapy alone** (n=92)
- **Bevacizumab and chemotherapy** (n=92)

Adjusted hazard ratio 0.70 (95% CI: 0.52–0.95)

P = 0.010 (stratified log-rank test)

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**Overall Survival (OS)**

- **Chemotherapy alone** (n=92)
- **Bevacizumab and chemotherapy** (n=92)

Adjusted hazard ratio 0.77 (95% CI: 0.56–1.06)

P = 0.043 (stratified log-rank test)

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**Number at risk**

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy alone</td>
<td>92</td>
<td>36</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab and chemotherapy</td>
<td>92</td>
<td>49</td>
<td>9</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

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ANTIANGIOGENIC TREATMENT

Arnold & Tabernero, Oncolpathol 2013
VELOUR Phase III Trial in Second-line Metastatic Colorectal Cancer

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

**Patients with metastatic colorectal cancer after failure of an oxaliplatin-based regimen**

**Randomization:** 1:1

**Groups:**
- 600 pts
  - Aflibercept 4 mg/kg IV + FOLFIRI q 2 weeks
- 600 pts
  - Placebo + FOLFIRI q 2 weeks

**Endpoints:**
- **Primary Endpoint:** OS
- **Secondary Endpoints:** ORR, PFS, safety, PK

OS: VELOUR study

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>HR (95.34% CI) vs Placebo/FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>t ≤ 6</td>
<td>0.860 (0.664-1.114)</td>
</tr>
<tr>
<td>6 &lt; t ≤ 12</td>
<td>0.838 (0.673-1.043)</td>
</tr>
<tr>
<td>12 &lt; t ≤ 18</td>
<td>0.782 (0.582-1.050)</td>
</tr>
<tr>
<td>t &gt; 18</td>
<td>0.676 (0.463-0.988)</td>
</tr>
</tbody>
</table>

RAISE: Study Design

Randomize (1:1)

Progression during or after bevacizumab, oxaliplatin, and a fluoropyrimidine

*Stratification factors:
  - Geographic regions
  - KRAS mutation status
  - Time to disease progression after beginning first-line therapy

Sample size assumptions
  - Hazard ratio of 0.8
  - Median overall survival of 10 months in the control arm vs 12.5 months with ramucirumab with a 2-sided α level of 0.05
  - Enrollment of 1050 patients with 756 events for 85% power
  - Gatekeeping from OS to PFS to ORR

Ramucirumab (8 mg/kg) and FOLFIRI* every 2 weeks per cycle N=525

Placebo and FOLFIRI* every 2 weeks per cycle N=525

Treatment until disease progression or unacceptable toxicity

Primary endpoint: Overall survival

Secondary endpoints: PFS, ORR, PRO, Safety, PK, IG

Abbreviations: IG=immunogenicity; PFS=progression-free survival; PK=pharmacokinetics; OS=overall survival; ORR=objective response rate.

*Irinotecan: 180 mg/m²; Folinic acid: 400 mg/m²; 5-Fluorouracil: 400 mg/m² bolus, followed by 2400 mg/m² administered intravenously over 48 to 48 hours (continuously).

Tabenero et al, GI Cancer Symposium 2015
Ramucirumab: Ensayo RAISE

# Anti-Angiogenic Strategies Result in Limited Improvements When Combined with 2nd Line Chemotherapy

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>RR</strong></td>
<td>BV 22.7 vs. 8.6%*</td>
<td>BV 5% vs. C 3%</td>
<td>Afl. 19.8% vs. C 11.1%*</td>
<td>Ram 13.4% vs. C 12.5%</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>BV 7.3 vs. 4.7 m*</td>
<td>BV 5.7 vs. C 4.1 m*</td>
<td>Afl. 6.9 vs. C 4.7 m*</td>
<td>Ram 5.7 vs. C 4.5 m*</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>BV 12.9 vs. 10.8 m*</td>
<td>BV 11.2 vs. C 9.8 m*</td>
<td>Afl. 13.5 vs. C 12 m*</td>
<td>Ram 13.3 vs. C 11.7 m*</td>
</tr>
<tr>
<td></td>
<td>HR = 0.61</td>
<td>HR = 0.68</td>
<td>HR = 0.76</td>
<td>HR = 0.79</td>
</tr>
</tbody>
</table>

*p < 0.05

PERMAD Trial: Determination of markers for (early) angiogenic switch

Biological

Bevacizumab

Aflibercept

Chemo

CHEMO A

CHEMO B

N=60

1st-line

2nd-line

Conventional switch of Chemo and Biological at timepoint of PD

Chemo A/B = FP + Ox/Iri

Assessment of CAF every 2 weeks and RECIST every 8 weeks

CI: Seufferlein, Stein, Arnold
PERMAD Trial: Randomized part

Patients with marker change and at least SD (RECIST)

1st-line

Biological

Bevacizumab

CHemo A

n=120

Biological

Bevacizumab

CHemo A

2nd-line

Chemo

Aflibercept

CHemo B

A

Conventional switch of Chemo and Biological at timepoint of PD

B

marker-driven early switch of Biological and conventional switch of Chemo at timepoint of PD

CI: Seufferlein, Stein, Arnold

Chemo A/B = FP + Ox/iri

Arnold D. ESMO 2016
ANTI-angiogenic treatment → Anti-EGFR

1st line
- Cytotoxic doublet\(^1\) + bevacizumab

2nd line
- Cytotoxic doublet\(^1\) + bevacizumab or aflibercept\(^3\)

3rd line
- Irinotecan or FOLFIRI + anti-EGFR antibody\(^2\)

4th line
- Regorafenib

\(^1\) cytotoxic doublets: fluoropyrimidine + oxaliplatin or irinotecan; \(^2\) Ras wild type; \(^3\) aflibercept only in combination with FOLFIRI
# EPIC: Phase III Trial of Cetuximab Plus Irinotecan After Fluoropyrimidine and Oxaliplatin Failure in Patients With Metastatic Colorectal Cancer

Alberto F. Sobrero, Joan Maurel, Louis Fehrenbacher, Werner Scheithauer, Yousif A. Abubakr, Manfred P. Lutz, M. Eugenia Vega-Villegas, Cathy Eng, Ernst U. Steinhauser, Jana Prausova, Heinz-Josef Lenz, Christophe Borg, Gary Middleton, Hendrik Kröning, Gabriele Luppi, Oliver Kisker, Angela Zubel, Christiane Langer, Justin Kopit, and Howard A. Burris III

<table>
<thead>
<tr>
<th></th>
<th>ERBITUX + irinotecan (n=648)</th>
<th>Irinotecan (n=650)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>16%</td>
<td>4%</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PFS meses</td>
<td>4.0</td>
<td>2.6</td>
<td>0.69</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>OS, meses</td>
<td>10.7</td>
<td>10.0</td>
<td>0.975</td>
<td>0.71</td>
</tr>
</tbody>
</table>

20% K-ras

13% BV previo

47% CET

Randomized Phase III Study of Panitumumab With Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) Compared With FOLFIRI Alone As Second-Line Treatment in Patients With Metastatic Colorectal Cancer


Metastatic CRC (n=1186) 1:1

Stratification by:
- ECOG score: 0-1 vs. 2
- Prior oxaliplatin exposure for mCRC
- Prior bevacizumab exposure for mCRC

- Study endpoints: PFS/OS (co-1°); ORR, safety, HRQoL

FOLFIRI (Q2W) + panitumumab 6 mg/kg (Q2W*)

End of treatment

Long term follow up

**PFS (KRAS WT, Prior Bevacizumab Treatment)**

### Prior Bevacizumab

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events n (%)</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab+ FOLFIRI (n=55)</td>
<td>31 (56)</td>
<td>5.8 (5.2–6.7)</td>
</tr>
<tr>
<td>FOLFIRI (n=60)</td>
<td>46 (77)</td>
<td>3.7 (3.5–5.3)</td>
</tr>
</tbody>
</table>

HR=0.71 (95% CI: 0.45–1.13)

* p-value=0.150

### Primary Analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events n (%)</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab+ FOLFIRI (n=303)</td>
<td>178 (59)</td>
<td>5.9 (5.5–6.7)</td>
</tr>
<tr>
<td>FOLFIRI (n=294)</td>
<td>203 (69)</td>
<td>3.9 (3.7–5.3)</td>
</tr>
</tbody>
</table>

HR=0.73 (95% CI: 0.59–0.90)

* p-value=0.004

\[ \Delta 2.0 \]

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* Analysis based upon the primary analysis data set
SPIRITT Trial

FOLFIRI + Panitumumab or Bevacizumab in 2nd-line Treatment of KRAS WT mCRC (Open Label, Phase 2)


mCRC after failure of 1st-line ox-based CT with bevacizumab (≥4 doses) (n=182)

R

1:1

FOLFIRI (Q2W) +
panitumumab 6 mg/kg (Q2W)

FOLFIRI (Q2W) +
bevacizumab 5 mg/kg or 10 mg/kg (Q2W) (Institutional standard dose)

Stratification by:
- Reason for 1st-line treatment failure (progression vs. toxicity)
- Intended bevacizumab dose (5mg/kg vs. 10 mg/kg)

Study endpoint: PFS* (1°); OS, ORR, TTP, safety, exploratory biomarker analysis

*PFS, progression-free survival; defined as time from date of randomisation to date of first radiographic disease (per modified RECIST v1.0), or death within 60 days after the last evaluable tumour assessment or randomisation (whichever is later). Subjects not meeting the criteria by the cut-off date were censored at the last evaluable tumour assessment date;
SPIRITTT Trial

PFS and OS

Panitumumab + FOLFIRI (n=91) vs Bevacizumab + FOLFIRI (n=91)

**PFS**

- **HR = 1.01 (95%CI: 0.68–1.50)**

**OS**

- **HR = 1.06 (95%CI: 0.75–1.49)**


ORR: 32% vs 19%
PRODIGE-18 trial

Hiret et al, ASCO 2016
Anti-EGFR treatment ---- Anti-angiogenic treatment

A: Scenario 1
- 1st line: Cytotoxic doublet\(^1\) + bevacizumab
- 2nd line: Cytotoxic doublet\(^1\) + bevacizumab or aflibercept\(^3\)
- 3rd line: Irinotecan or FOLFIRI + anti-EGFR antibody\(^2\)
- 4th line: Regorafenib

B: Scenario 2
- 1st line: Cytotoxic doublet\(^1\) + bevacizumab
- 2nd line: Cytotoxic doublet\(^1\) + anti-EGFR antibody\(^2\)
- 3rd line: Regorafenib

C: Scenario 3
- 1st line: Cytotoxic doublet\(^1\) + anti-EGFR antibody\(^2\)
- 2nd line: Cytotoxic doublet\(^1\) + bevacizumab or aflibercept
- 3rd line: Regorafenib

\(^1\) cytotoxic doublets: fluoropyrimidine + oxaliplatin or irinotecan; \(^2\) Ras wild type; \(^3\) aflibercept only in combination with FOLFIRI
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


![Graph C](image1.png)

**RAS wild-type population**

<table>
<thead>
<tr>
<th>Events</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>144</td>
<td>10.4 months</td>
<td>9.5-12.2</td>
</tr>
<tr>
<td>143</td>
<td>10.2 months</td>
<td>9.3-11.5</td>
</tr>
</tbody>
</table>

![Graph D](image2.png)

**Overall survival**

<table>
<thead>
<tr>
<th>Events</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>33.1 months</td>
<td>24.5-39.4</td>
</tr>
<tr>
<td>110</td>
<td>25.6 months</td>
<td>22.7-28.6</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>FOLFIRI plus cetuximab</th>
<th>FOLFIRI plus bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI plus cetuximab</td>
<td>171</td>
<td>171</td>
</tr>
<tr>
<td>FOLFIRI plus bevacizumab</td>
<td>171</td>
<td>171</td>
</tr>
<tr>
<td>Number at risk</td>
<td>FOLFIRI plus cetuximab</td>
<td>FOLFIRI plus bevacizumab</td>
</tr>
<tr>
<td>FOLFIRI plus cetuximab</td>
<td>128</td>
<td>127</td>
</tr>
<tr>
<td>FOLFIRI plus bevacizumab</td>
<td>68</td>
<td>69</td>
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</table>
Impact of Subsequent Therapies on Outcome of the FIRE-3/AIO KRK0306 Trial: First-Line Therapy With FOLFIRI Plus Cetuximab or Bevacizumab in Patients With KRAS Wild-Type Tumors in Metastatic Colorectal Cancer


B

<table>
<thead>
<tr>
<th>Arm</th>
<th>Months (95% CI)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.7 (5.8 to 7.4)</td>
<td>105/138</td>
<td>76.1</td>
</tr>
<tr>
<td>B</td>
<td>4.8 (4.2 to 5.8)</td>
<td>110/137</td>
<td>80.3</td>
</tr>
</tbody>
</table>

Log-rank P = .003
Hazard ratio, 0.67 (0.51 to 0.87)

D

<table>
<thead>
<tr>
<th>Arm</th>
<th>Months (95% CI)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>17.6 (15.0 to 21.7)</td>
<td>88/138</td>
<td>63.8</td>
</tr>
<tr>
<td>B</td>
<td>14.8 (10.3 to 16.8)</td>
<td>106/137</td>
<td>77.4</td>
</tr>
</tbody>
</table>

Log-rank P = .0021
Hazard ratio: 0.64 (0.48 to 0.85)

No. at risk
Arm A 138
Arm B 137

Time (months)
STRATEGIC-1: GERCOR

Arm A
- **FOLFIRI + cetuximab**
  - First-line
  - Oxaliplatin-based + bevacizumab
  - Second-line
  - Off-protocol. No standard option in patients refractory to:
    - Both irinotecan & oxaliplatin,
    - Both anti-angiogenic & anti-EGFR agents
  - Third-line
    - Bevacizumab-based

Arm B
- **OPTIMOX + bevacizumab**
  - First-line
  - Irinotecan-based + bevacizumab
  - Second-line
  - Anti-EGFR agent +/- Irinotecan

Arnold D. ESMO 2016
ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

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].