Metastatic Colorectal Cancer

What to do after progression?

JY Douillard MD, PhD
Professor of Medical Oncology
Integrated Center of Oncology R Gauducheau
Nantes France
mCRC: what to do after progression

• Most of patients with mCRC will progress under treatment or after a treatment break

• Several drugs and drug combination are available

• Anti EGFR have single agent activity and in combination with chemotherapy. They work in all lines in RAS wt mCRC

• Bevacizumab has no activity as single agent but improve outcome in combination with chemotherapy.

• Most patients will receive multiple lines of treatment
mCRC: what to do after progression

• Several factors should be considered if an additional line is needed:
  – Patient’s desire to continue treatment
  – Patient’s condition (PS) and comorbidities
  – Tolerance to last line or residual toxicity
  – Safety of the planned combination
  – Drugs previously used
  – Strategy/schedule use in previous lines
mCRC: what to do after progression

• The concept of lines should be revised:
  – Drug re-introduction
  – Drug continuation
  – Intercalating other treatment method
    • Surgery (even palliative)
    • Radiation
    • Radio-frequency
    • Radio-immunotherapy

• Adding several treatment modality illustrate the concept of Continuum of care
mCRC: what to do after progression

- HOW TO DEFINE PROGRESSION?
  - In clinical trials: RECIST is the Gold Standard
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Eisenhauer et al EJC 2009; 45: 228
RECIST

• Essentially used for evaluation of new drugs/regimen in clinical trials

• A tool to measure efficacy in a standardized manner
  – To obtain a Response Rate
  – To evaluate Progression-Free Survival

• Not always easy to use
  – Bone lesions
  – Pleural, peritoneal, pericardial effusion
  – Best for round-shaped lesions

• Is it reliable for treatment modification/decision in clinical practice?
RECIST 1.2

Real progression as compared to baseline

Time

+ 20%
Definition of progression in clinical practice

• Target lesion size should be considered

• Other parameters are important as well:
  – Symptoms/quality of life
  – Clinical examination
  – Tolerance to treatment/acceptability
  – Patient opinion
  – Growth rate
  – Tumor markers (CEA, Ca 19.9)

• Daily clinical practice is not clinical research practice
What to do after progression?

- Progression may be established on multiple parameters
- Once established:
- Multiple options are available
Conventional and nonconventional (drug rechallenge and treatment beyond progression) therapy regimens in medical oncology

Kuczynski, E. A. et al. (2013) Drug rechallenge and treatment beyond progression—implications for drug resistance
**Sequential 1\textsuperscript{st} and 2\textsuperscript{nd} Line Combinations**

Randomized, multicentric, open-label, prospective, phase III trial

- **Arm A**
  - FOLFIRI
  - CPT-11 180 mg/m\textsuperscript{2} IV + simplified LV5FU

- **Arm B**
  - FOLFOX6
  - Oxaliplatin 100 mg/m\textsuperscript{2} IV + simplified LV5FU

*until progression*

Efficacy Endpoints

Time to progression in 1\textsuperscript{st} line

- Folfiri 8.5
- Folfox 8.1

Logrank $p = 0.21$

Time to progression in 2\textsuperscript{nd} line

- Folfiri 2.5
- Folfox 4.1
## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFIRI</td>
<td>FOLFOX</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>109</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>ORR (CR) %</td>
<td>53 (3)</td>
<td>15</td>
<td>0.68</td>
</tr>
<tr>
<td>ORR+SD %</td>
<td>79</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Median TTP</td>
<td>14.4</td>
<td>11.5</td>
<td>0.65</td>
</tr>
<tr>
<td>Median surv</td>
<td>20.4</td>
<td>21.5</td>
<td>0.90</td>
</tr>
<tr>
<td>Progression-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>free at 15 mo</td>
<td>49</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>
"stop and go" strategy (GISCAD)

mCCR 1st line (n=331)

FOLFIRI STOP 2 months FOLFIRI 2 months (A)

FOLFIRI FOLFIRI (B)

No progression

Kaplan–Meier curves for overall survival (A) and progression-free survival (B).

16.9 vs 17.6 m

6.2 vs. 6.5 m

Oxaliplatin reintroduction at progression after FOLFOX 1st line

- 29 patients initially treated with Folfox (2, 3, 5, 6, 7)
  - 1st-line ORR: 24/29, SD 4/29, PD 1/29
  - 16 patients receive intervening therapy before Folfox reintroduction
    - 5FU-LV2, Irinotecan
    - Median Oxali-free interval 48 w
  - Median PFS after reintroduction: 11 weeks
  - Median OS after reintroduction: 36 weeks

Conventional and nonconventional (drug rechallenge and treatment beyond progression) therapy regimens in medical oncology

Kuczynski, E. A. et al. (2013) Drug rechallenge and treatment beyond progression—implications for drug resistance
Reintroduction of the same regimen after progression following a break

- Relapses may be termed « sensitive » rather than « resistant » after initial control

- Treatment-free interval should be considered
  - The longer the time to progression, the greater the chance of a response to re-treatment with the same regimen
Oxaliplatin reintroduction at progression after FOLFOX in 1st line

- 29 patients initially treated with Folfox (2, 3, 5, 6, 7)
  - 1st-line ORR: 24/29, SD 4/29, PD 1/29
  - 13 patients did not receive therapy until PD
    - Median treatment-free interval: 12 weeks (3-99w)
    - 12/13 had a disease control after reintroduction
  
  - Median PFS after reintroduction: 27 weeks
  - Median OS after reintroduction: 58 weeks

**CAIRO-3 (phIII) Design**

- **Pts mCCR L1** (n=558)
  - PS 0/1
  - Non resectable

- **Arm A**
  - Observation
  - Avastin + XELOX (x6)

- **Arm B**
  - Avastin + capecitabine

- **Primary Endpoint**: PFS after reintroduction of induction CT (PFS2)
- **Secondary Endpoints**: PFS1, OS, TTP2, ORR, tolerance
- **Sponsor**: Dutch Colorectal Cancer Group (DCCG)
- **Treatments**: bevacizumab: 2,5 mg/kg/week (eq.) / Capecitabine: 625mg/m² x2/d

---

**Koopman M et al. ASCO 2013 (abst. 3502)**
Re-introduction of 1st-line regimen: CAIRO 3

Results: PFS2 primary endpoint

SD or better after 6 cycles CAPOX-B

R

observation

PD

Re-introduction CAPOX-B

capecitabine + bevacizumab

PD

Primary endpoint: PFS2

- time from randomization to progression upon re-introduction of CAPOX-B
- PFS2 is considered to be equal to PFS1 for patients in whom CAPOX-B is not reintroduced after PFS1 for any reason
CAIRO-3 (phIII) Patients Disposition

558 patients accrued

- 279 patients
  - Arm A “observation”
    - 212 patients (76%)
      - CAPOX-Bev
    - 67 patients (24%)
      - No CAPOX-Bev

- 279 patients
  - Arm B “maintenance”
    - 131 patients (47%)
      - CAPOX-Bev
    - 148 patients (53%)
      - No CAPOX-Bev

Koopman M et al. ASCO 2013 (abst. 3502)
Re-introduction of 1st-line regimen: CAIRO 3
Conventional and nonconventional (drug rechallenge and treatment beyond progression) therapy regimens in medical oncology

Kuczynski, E. A. et al. (2013) Drug rechallenge and treatment beyond progression—implications for drug resistance
Continuous Blockade of Angiogenesis

Bevacizumab Beyond Progression (BBP)

- 2 randomized studies:
  - TML\(^1\)
  - BEBYP\(^2\)

ML18147 Study Design (phase III)

BEV + standard first-line CT (either oxaliplatin or irinotecan-based) (n=820)

PD

Randomise 1:1

CT switch:
Oxaliplatin → Irinotecan
Irinotecan → Oxaliplatin

Standard second-line CT (oxaliplatin or irinotecan-based) until PD

BEV (2.5 mg/kg/wk) + standard second-line CT (oxaliplatin or irinotecan-based) until PD

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)

BEBYP: Study Design

**I-line CT * + BV**
- Center
- PS 0/1-2
- CT-free interval (> vs ≤ 3 mos)
- II-line CT

**A. Second-line CT §**
- FOLFIRI
- FOLFOX
- FOLFOXIRI
- Fluoropyrimidine mono-tx

**B. Second-line CT § + BV**
- FOLFIRI
- mFOLFOX-6

*Study conducted in 19 Italian centers*

Supported by AIFA

Masi G, ESMO Vienna 2012  LBA 17.
### How Does BEBYP Compare with TML?

<table>
<thead>
<tr>
<th>TML</th>
<th>BEBYP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Randomized phase III</td>
<td>• Randomized phase II</td>
</tr>
<tr>
<td>• N= 820</td>
<td>• N=262 planned</td>
</tr>
<tr>
<td>• Complete accrual</td>
<td>• Terminated early at 184 pt</td>
</tr>
<tr>
<td>• All Bev. Pre-treated 1st line</td>
<td>• All Bev. Pre-treated 1st line</td>
</tr>
<tr>
<td>• 2(^{nd}) line w/wo Bev</td>
<td>• 2(^{nd}) line w/wo Be</td>
</tr>
<tr>
<td>• 1st EP: OS since rando</td>
<td>• 1st EP: PFS since rando</td>
</tr>
<tr>
<td>• 2(^{nd}) EP:</td>
<td>• 2(^{nd}) EP:</td>
</tr>
<tr>
<td>– PFS</td>
<td>– OS (immature)</td>
</tr>
<tr>
<td>– ORR</td>
<td>– ORR</td>
</tr>
<tr>
<td>– Safety</td>
<td>– Safety</td>
</tr>
</tbody>
</table>

Both studies evaluated the use of Bevacizumab beyond progression
## How Does BEBYP Compare with TML? Patient Populations

<table>
<thead>
<tr>
<th>TML</th>
<th>BEBYP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td>– PD&gt;3m after last Bev</td>
<td>– PD after 3m or during 1st line CT+Bev</td>
</tr>
<tr>
<td>– 1st line PFS &lt; 3 m</td>
<td>– Or 3m after Folfoxiri Bev</td>
</tr>
<tr>
<td>– 1st line Bev&lt; 3 consecutive m</td>
<td></td>
</tr>
<tr>
<td><strong>1st line PFS</strong></td>
<td><strong>1st line PFS</strong></td>
</tr>
<tr>
<td>– ≤ 9m: 55%</td>
<td>– 10.3 m</td>
</tr>
<tr>
<td>– &gt; 9m: 45%</td>
<td></td>
</tr>
<tr>
<td><strong>Post-study treatment (C/CB)</strong></td>
<td><strong>Post-study treatment (C/CB)</strong></td>
</tr>
<tr>
<td>– Bev: 12%/11%</td>
<td>– Bev: 1%/3%</td>
</tr>
<tr>
<td>– Anti EGFR: 39%/41%</td>
<td>– Anti EGFR: 46%/32%</td>
</tr>
</tbody>
</table>
How Does BEBYP Compare with TML?

**PFS Analysis**

<table>
<thead>
<tr>
<th></th>
<th>CT (n=410)</th>
<th>BEV + CT (n=409)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>410</td>
<td>409</td>
</tr>
<tr>
<td>6</td>
<td>119</td>
<td>189</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>36</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**HR**: 0.68
(95% CI: 0.59–0.78)
p < 0.0001 (log-rank test)

**HR**: 0.65
(95% CI 0.48–0.89)
p = 0.0062

4.97 m vs 6.77 m
How Does BEBYP Compare with TML?

ORR Analysis

<table>
<thead>
<tr>
<th></th>
<th>TML</th>
<th>BEBYP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT</td>
<td>p</td>
</tr>
<tr>
<td>ORR %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.31</td>
<td>5</td>
</tr>
<tr>
<td>DCR</td>
<td>54</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
How does BEBYP compare with TML?

OS analysis

TML

BEBYP

HR: 0.81

(95% CI: 0.69–0.94)

p=0.0062 (log-rank test)

Overall Survival

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>CT (70 events) median OS = 15.9 mos</th>
<th>CT+ B (66 events) median OS = 14.3 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>18</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>24</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>30</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>36</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>42</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>48</td>
<td>1.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th>CT</th>
<th>BEV + CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>410</td>
<td>409</td>
</tr>
<tr>
<td>293</td>
<td>328</td>
</tr>
<tr>
<td>162</td>
<td>188</td>
</tr>
<tr>
<td>51</td>
<td>64</td>
</tr>
<tr>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

9.8

11.2
How Does BEBYP Compare with TML? Sub-group Analysis

• All sub groups studied in both TML and BEBYP benefited from Bevacizumab continuation on PFS
• No data on OS for BEBYP

• Partial population analysis for Kras:
  – In both TML and BEBYP the benefit of Bev was independant of Kras for PFS
  – but not on OS for Kras mutant as opposed to wild-type (TML only)
TML: PFS in the KRAS Population

KRAS wild type

Interaction test by KRAS status is negative (p=0.4436)

KRAS mutant

HR: 0.61
95% CI: 0.49–0.77
p<0.0001 (log-rank test)

HR: 0.70
95% CI: 0.56–0.89
p=0.0027 (log-rank test)

Courtesy from E Van Cutsem WCGIC Barcelona June 2012.
Survival according to the treatment group and tumor KRAS mutation status: (A) PFS and (B) OS.

241/316 received anti-EGFR in later lines.

Figure 1 Conventional and nonconventional (drug rechallenge and treatment beyond progression) therapy regimens in medical oncology

Kuczynski, E. A. et al. (2013) Drug rechallenge and treatment beyond progression—implications for drug resistance
Proposal for sequence of salvage-chemotherapy.


© The Author 2012. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email: journals.permissions@oup.com.
What to do after progression?

• Most of the patients with mCRC are not curable
• Quality of life should be considered as well as quality

• Continuous exposure during all the surviving time is not feasible due to toxicity and compliance and is not demonstrated to be beneficial on OS

• Numerous alternative strategies are available, most often offering treatment breaks that will benefit to quality of life

• Patient opinion and desires must be considered for decision making