ESMO Preceptorship colorectal cancer
Singapore 28-29th March 2015

Session 7

• The continuum of care in CRC vs. lines of treatment
• Appropriate use of new agents (Aflibercept, Regorafenib)
• Re-introduction of regimens
The continuum of care in CRC vs. lines of treatment

- 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
- Median Overall Survival now reaches 24-30 months and patients can hardly receive continuous chemotherapy
The continuum of care in CRC vs. lines of treatment

• 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
The continuum of care in CRC vs. lines of treatment

• The concept of lines should be revisited with concepts:
  – 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
HOW TO DEFINE PROGRESSION?
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).
**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

+ 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

Conventional lines of therapy
- Different agents are given sequentially and switched due to disease progression, unacceptable toxicity or patient choice.
- Therapy 1 is stopped after a set number of cycles or maximal response. Patient relapses off therapy and is switched to therapy 2.

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

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

Arm A

Arm B

Efficacy Endpoints

Logrank $p = 0.21$

Median (months)
- Folfiri 8.5
- Folfox 8.1

Months

Probability

0.0 0.2 0.4 0.6 0.8 1.0

0 4 8 12 16 20 24 28 32

Median (months)
- Folfiri 2.5
- Folfox 4.1

Months

Probability

0.0 0.2 0.4 0.6 0.8 1.0

0 6 12 18
# 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-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

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

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
The continuum of care in CRC vs. lines of treatment

Continuous versus intermittent chemotherapy strategies in metastatic colorectal cancer: a systematic review and meta-analysis

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Cancer Care Ontario’s Gastrointestinal Disease Site Group

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Table 1. Characteristics of identified randomized, controlled trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary outcome</th>
<th>Type of trial</th>
<th>Treatment</th>
<th>Number of patients randomized (evaluated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-agent trial</td>
<td>Overall survival</td>
<td>Superiority</td>
<td>Intermittent (12 weeks deGraaf et al. [16] or Leckie et al. [17] or both; CF, retart at PD) or Continuous (12 weeks deGraaf et al. [16] or Leckie et al. [17] or both and until PD)</td>
<td>178</td>
</tr>
<tr>
<td>Combination trials: Intermittent chemotherapy with 5-FU maintenance therapy</td>
<td>Duration of disease control</td>
<td>Superiority</td>
<td>Intermittent (POLP07, 12 weeks; AV-5-FU, 24 weeks; POLP07, 12 weeks)</td>
<td>110</td>
</tr>
<tr>
<td>Godley et al. (CONCOFT) [7], Abstract</td>
<td>Time-to-treatment failure</td>
<td>Superiority</td>
<td>Intermittent (mPOLP07 + BEV every 2 weeks until PD) or BEV every 2 weeks with and without oxaliplatin and CA-Mg until PD</td>
<td>180 (139) (in total)</td>
</tr>
<tr>
<td>Combination trials: Intermittent chemotherapy with no maintenance therapy</td>
<td>Overall survival</td>
<td>Noninferiority</td>
<td>Intermittent (POLF07, 12 weeks; CF, retart POLF07 at PD)</td>
<td>20</td>
</tr>
<tr>
<td>Chihara et al. (OPTIMOX2) [9]</td>
<td>Duration of disease control</td>
<td>Superiority</td>
<td>Intermittent (mPOLP07, 12 weeks; CF, retart mPOLP07 at PD, 12 weeks) or Continuous (mPOLP07, 12 weeks; AV-5-FU, retart mPOLP07 at PD, 12 weeks)</td>
<td>170 (104)</td>
</tr>
<tr>
<td>Addeo et al. (CISIN) [10]</td>
<td>Overall survival</td>
<td>Noninferiority</td>
<td>Intermittent (POLF07 or CapeOn, 12 weeks; CF, retart same chemo at PD)</td>
<td>19</td>
</tr>
<tr>
<td>Lahlou et al. [11]</td>
<td>Overall survival</td>
<td>Noninferiority</td>
<td>Intermittent (POLF07 every 2 weeks and 2 months on, 2 months of until PD) or Continuous (POLF07 every 2 weeks until PD)</td>
<td>170 (146)</td>
</tr>
<tr>
<td>Koopman et al. (CARIOS) [12], Abstract</td>
<td>Progression-free survival</td>
<td>Superiority</td>
<td>Intermittent (BEV + CapeOn, 8 weeks; CF, retart BEV + CapeOn at PD)</td>
<td>279 (257)</td>
</tr>
<tr>
<td>Combination trials: Intermittent chemotherapy with a biologic maintenance therapy</td>
<td>Progression-free survival</td>
<td>Noninferiority</td>
<td>Intermittent (BEV + CapeOn, 8 weeks; BEV only until PD) or Continuous (BEV + CapeOn until PD)</td>
<td>281</td>
</tr>
<tr>
<td>Due-Abele et al. (MACH3) [13]</td>
<td>Progression-free survival</td>
<td>Noninferiority</td>
<td>Intermittent (Cetuximab + FOLFOX16, 16 weeks) or Continuous (Cetuximab + FOLFOX16 at PD)</td>
<td>170</td>
</tr>
<tr>
<td>Tusa et al. (NORDIC V1C) [4]</td>
<td>Progression-free survival</td>
<td>Superiority</td>
<td>Intermittent (FOLFOX16 until PD or until progression or toxicity)</td>
<td>158</td>
</tr>
<tr>
<td>Combination trials: Intermittent chemotherapy with fluoropyrimidines and biologic maintenance chemotherapy</td>
<td>Progression-free survival</td>
<td>Superiority</td>
<td>Intermittent (BEV + CapeOn, 18 weeks; BEV + cap until PD)</td>
<td>61</td>
</tr>
<tr>
<td>Yelin et al. [15]</td>
<td>Progression-free survival</td>
<td>Superiority</td>
<td>Intermittent (BEV + CapeOn, Continuous (BEV + CapeOn until PD)</td>
<td>62</td>
</tr>
</tbody>
</table>
Meta-analysis for overall survival: all trials.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
<th>Hazard Ratio IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maughan 2003</td>
<td>-0.1393</td>
<td>0.1166</td>
<td>8.8%</td>
<td>0.87 [0.69, 1.09]</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>OPTIMOX1 (Tournigand 2006)</td>
<td>-0.0726</td>
<td>0.1104</td>
<td>9.9%</td>
<td>0.93 [0.75, 1.15]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Alexopoulos 2006</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>CONcePT (Grothey 2008)</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>OPTMOX2 (Chibaudel 2009)</td>
<td>0.131</td>
<td>0.1625</td>
<td>4.5%</td>
<td>1.14 [0.83, 1.57]</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>COIN (Adams 2011)</td>
<td>0.0807</td>
<td>0.0565</td>
<td>37.6%</td>
<td>1.08 [0.97, 1.21]</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>Labianca 2011</td>
<td>-0.0943</td>
<td>0.1195</td>
<td>8.4%</td>
<td>0.91 [0.72, 1.15]</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>MACRO (Diaz-Rubio 2012)</td>
<td>0.0488</td>
<td>0.1084</td>
<td>10.2%</td>
<td>1.05 [0.85, 1.30]</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>NORDIC VII (Tveit 2012)</td>
<td>0.0296</td>
<td>0.1246</td>
<td>7.7%</td>
<td>1.03 [0.81, 1.31]</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Yalcin 2013</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>CAIRO3 2014</td>
<td>0.1133</td>
<td>0.097</td>
<td>12.8%</td>
<td>1.12 [0.93, 1.35]</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.03 [0.96, 1.10]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 6.01, df = 7 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.38)


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Continuous Blockade of Angiogenesis

Bevacizumab Beyond Progression (BBP)

• 2 randomized studies:
  – TML\(^1\)
  – BEBYP\(^2\)
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)

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

PD ➔ Randomise 1:1 ➔
- 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

BEBYP: Study Design

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

A. Second-line CT §

B. Second-line CT § + BV

* • FOLFIRI
   • FOLFOX
   • FOLFOXIRI
   • Fluoropyrimidine mono-tx

§ • FOLFIRI
   • mFOLFOX-6

• Study conducted in 19 Italian centers

Supported by AIFA

Masi G, Annals of Oncology 00: 1–8, 2015
doi:10.1093/annonc/mdv012
Bevacizumab beyond progression
PFS Analysis

TML (2nd EP)

BEBYP (1st EP)

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

HR=0.70
(95% CI 0.48-0.89)
p=0.01

5 m
6.8 m

Bevacizumab beyond progression
OS analysis

TML

BEBYP

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

Survival in TML by treatment group and tumor KRAS mutation status: (A) PFS and (B) OS.

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

**a** Conventional lines of therapy

1. Different agents are given sequentially and switched due to disease progression, unacceptable toxicity or patient choice.

2. Therapy 1 is stopped after a set number of cycles or maximal response. Patient relapses off therapy and is switched to therapy 2.

3. Therapy 1 is administered intermittently in a pre-planned schedule. Disease progression does not occur at each treatment cycle.

Two lines of therapy 1 and 1’ are similar. They have the same mechanism of action or consist of slightly different drug combinations.

**b** Drug rechallenge

1. After progressing on therapy 1, the patient receives a different intervening therapy and is then rechallenged with therapy 1.

2. Therapy 1 is stopped and then disease progresses/relapses. The patient is rechallenged with the same therapy.

**c** Continuation of treatment beyond progression

1. Therapy 1 is continued without a therapy break (or minimal therapy break) despite disease progression. The therapy combining with 1 (2) is switched at progression to a new therapy (3).


Strategic scenarios in the continuum of care of metastatic colorectal cancer.

A: Scenario 1
- Cytotoxic doublet\(^1\) + bevacizumab

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

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

1st line
- Cytotoxic doublet\(^1\) + bevacizumab or afiblercept\(^3\)

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

3rd line
- Regorafenib

4th line
- Regorafenib

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

Session 7
Metastatic colorectal cancer II

Appropriate use of new agents
(Aflibercept, Regorafenib)
Session 7
Metastatic colorectal cancer II

• New drugs are regularly coming in the market
  – How do they contribute to the continuum of care
  – How do they compare to the pre-existing drugs
    • In terms of efficacy
    • In terms of toxicity

• What is the magnitude of the benefit?
  – Risk/benefit ratio?
  – Cost effectiveness?
Afibercept (Zaltrap®)

- Fusion protein of key domains from human VEGF receptors 1 and 2 with human IgG Fc
- Blocks all human VEGF-A isoforms, VEGF-B and placental growth factor (PIGF)
- High affinity – binds VEGF-A and PIGF more tightly than native receptors
- Contains human amino acid sequences

VELOUR Study Design

Metastatic Colorectal Cancer

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

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

Placebo IV, day 1 + FOLFIRI q2 weeks

Primary endpoint: Overall survival

Sample size: HR 0.8, 90% power and a 2-sided type I error 0.05

Final analysis of OS: Analyzed at 863th death event using a 2-sided nominal significance level of 0.0466 (α spending function)
Kaplan-Meier curves for overall survival (OS) and progression-free survival (PFS) in the primary analysis population.
# VELOUR: Tolerance profile

## Table 3. Summary of the Most Frequent Adverse Events (Incidence ≥ 20% or ≥ 5% Higher in aflibercept arm), Other Anti-VEGF–Associated Events, and Most Frequent Biologic Abnormalities: Safety Population

<table>
<thead>
<tr>
<th>Adverse Event*</th>
<th>Placebo/FOLFI R (n = 605)</th>
<th>Aflibercept/FOLFI R (n = 611)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Any</td>
<td>97.9</td>
<td>45.1</td>
</tr>
<tr>
<td>Diarrhea (PT)</td>
<td>56.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Asthenic conditions (HLT)</td>
<td>50.2</td>
<td>10.4</td>
</tr>
<tr>
<td>Stomatitis and ulceration (HLT)</td>
<td>34.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Nausea (PT)</td>
<td>54</td>
<td>3.0</td>
</tr>
<tr>
<td>Infections and infestations (SOC)</td>
<td>32.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>19</td>
<td>1.7</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7.4</td>
<td>—</td>
</tr>
<tr>
<td>GI and abdominal pains (HLT)</td>
<td>29.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Vomiting (PT)</td>
<td>33.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Decreased appetite (PT)</td>
<td>23.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>14.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Alopecia (PT)</td>
<td>30.1</td>
<td>—</td>
</tr>
<tr>
<td>Dysphonia (PT)</td>
<td>3.3</td>
<td>—</td>
</tr>
<tr>
<td>Constipation (PT)</td>
<td>24.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Headache (PT)</td>
<td>8.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>4.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Other anti-VEGF–associated events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolic event</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Venous thromboembolic event</td>
<td>7.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Fistula from GI origin</td>
<td>0.3</td>
<td>—</td>
</tr>
<tr>
<td>Fistula from other than GI origin</td>
<td>0.2</td>
<td>—</td>
</tr>
<tr>
<td>GI perforation</td>
<td>0.5</td>
<td>0.2</td>
</tr>
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</table>

**Biologic abnormalities**

<table>
<thead>
<tr>
<th>Hematologic</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>91.1</td>
<td>3.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>56.3</td>
<td>19.1</td>
<td>10.4</td>
</tr>
<tr>
<td>Neutropenic complications</td>
<td>3.0</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**Nonhematologic**

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT increased</td>
<td>40.7</td>
<td>1.2</td>
<td>—</td>
</tr>
</tbody>
</table>

Eric Van Cutsem et al. JCO 2012;30:3499-3506
## Grade 3-5 adverse events

**TML (Bevacizumab) and Velour (Aflibercept)**

<table>
<thead>
<tr>
<th>Grade 3-4</th>
<th>TML</th>
<th>VELOUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>19.3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9</td>
<td>16.8</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3</td>
<td>13.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>NA</td>
<td>1.8</td>
</tr>
<tr>
<td>Infection</td>
<td>NA</td>
<td>12.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>19.3</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>ATE</td>
<td>NA</td>
<td>1.8</td>
</tr>
<tr>
<td>VTE</td>
<td>5</td>
<td>7.8</td>
</tr>
<tr>
<td>GI Fistula</td>
<td>NA</td>
<td>0.3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16</td>
<td>36.7</td>
</tr>
<tr>
<td>Neutropenic complications</td>
<td>NA</td>
<td>5.7</td>
</tr>
</tbody>
</table>
AFFIRM Study Design

1L mCRC (N=236)

Stratification factors:
- ECOG PS (0-1 vs 2)
- Adjuvant therapy
- Metastases (liver-only vs other organs, including liver)

Randomise

Aflibercept 4 mg/kg IV, day 1 + mFOLFOX6 q2 weeks

Non-comparative study

mFOLFOX6c q2 weeks

Disease Progression
Study cutoffa
Death

Disease Progression
Study cutoffa
Death

- Primary endpoint: 12-month PFSd
- Key secondary endpoints: PFS, OS, ORR, safety, translational medicine (biomarkers)

aCutoff date defined as 12 months after last patient randomization.
bStudy was not powered for statistical comparison between the 2 arms.
cInternal benchmark.
dPer IRC.
12-Month Progression-Free Survival by IRC

<table>
<thead>
<tr>
<th></th>
<th>mFOLFOX6 (n=111)</th>
<th>Aflibercept/mFOLFOX6 (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint: 12-month PFS,(^a) % (95% CI)</td>
<td>21.2 (12.2-30.3)</td>
<td>25.8 (17.2-34.4)</td>
</tr>
</tbody>
</table>

\(^a\)Study was not powered for statistical comparison between the 2 arms.


PFS 8.6 vs. 8.9 m
ORR 46 vs. 49 %
The issue of cost for continuous angiogenic blockade

First- and Second-Line Bevacizumab in Addition to Chemotherapy for Metastatic Colorectal Cancer: A United States–Based Cost-Effectiveness Analysis

Daniel A. Goldstein, Qiushi Chen, Turgay Ayer, David H. Howard, Joseph Lipscomb, Bassel F. El-Rayes, and Christopher R. Flowers

Results
Using bevacizumab in first-line therapy provided an additional 0.10 QALYs (0.14 life-years) at a cost of $59,361. The incremental cost-effectiveness ratio was $571,240 per QALY. Continuing bevacizumab beyond progression provided an additional 0.11 QALYs (0.16 life-years) at a cost of $39,209. The incremental cost-effectiveness ratio was $364,083 per QALY. In univariable sensitivity analyses, the variables with the greatest influence on the incremental cost-effectiveness ratio were bevacizumab cost, overall survival, and utility.

Conclusion
Bevacizumab provides minimal incremental benefit at high incremental cost per QALY in both the first- and second-line settings of metastatic colorectal cancer treatment.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology
Regorafenib (BAY 73-4506), an Oral Multikinase Inhibitor Targeting Multiple Tumor Pathways

![Chemical Structure of Regorafenib](image)

- **Inhibition of proliferation**
- **Inhibition of tumor microenvironment signaling**
- **Inhibition of neoangiogenesis**

<table>
<thead>
<tr>
<th>Biochemical Activity</th>
<th>Regorafenib IC$_{50}$ mean ± SD nmol/l (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR1</td>
<td>13 ± 0.4 (2)</td>
</tr>
<tr>
<td>Murine VEGFR2</td>
<td>4.2 ± 1.6 (10)</td>
</tr>
<tr>
<td>Murine VEGFR3</td>
<td>46 ± 10 (4)</td>
</tr>
<tr>
<td>TIE2</td>
<td>311 ± 46 (4)</td>
</tr>
<tr>
<td>PDGFR-β</td>
<td>22 ± 3 (2)</td>
</tr>
<tr>
<td>FGFR1</td>
<td>202 ± 18 (6)</td>
</tr>
<tr>
<td>KIT</td>
<td>7 ± 2 (4)</td>
</tr>
<tr>
<td>RET</td>
<td>1.5 ± 0.7 (2)</td>
</tr>
<tr>
<td>RAF-1</td>
<td>2.5 ± 0.6 (4)</td>
</tr>
<tr>
<td>B-RAF</td>
<td>28 ± 10 (6)</td>
</tr>
<tr>
<td>B-RAF$^{V600E}$</td>
<td>19 ± 6 (6)</td>
</tr>
</tbody>
</table>

CORRECT study design

- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - 2:1 randomization
  - Strat. factors: prior anti-VEGF therapy, time from diagnosis of mCRC, geographical region
- Global trial: 16 countries, 114 active centers
  - 1,052 patients screened, 760 patients randomized within 10 months
- Secondary endpoints: PFS, ORR, DCR
- Tertiary endpoints: duration of response / stable disease, QOL, pharmacokinetics, biomarkers

Grothey et al., Lancet 2012
Overall survival (primary endpoint)

Primary endpoint met prespecified stopping criteria at interim analysis (1-sided p<0.009279 at approximately 74% of events required for final analysis)

Hazard ratio: 0.77 (95% CI: 0.64–0.94)
1-sided p-value: 0.0052

Grothey et al. Lancet 2012
Overall survival (primary endpoint)

Primary endpoint met prespecified stopping criteria at interim analysis
(1-sided p<0.009279 at approximately 74% of events required for final analysis)

Grothey et al. Lancet 2012
Progression-free survival (secondary endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.9 mos</td>
<td>1.7 mos</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.9–2.1</td>
<td>1.7–1.7</td>
</tr>
</tbody>
</table>

Hazard ratio: 0.49 (95% CI: 0.42–0.58)
1-sided p-value: <0.000001

Grothey et al., Lancet 2012
**CORRECT: Adverse events in ≥10% of patients**

<table>
<thead>
<tr>
<th>Adverse event, %</th>
<th>Regorafenib + BSC arm n=500</th>
<th></th>
<th>Placebo + BSC arm n=253</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hand–foot skin reaction</td>
<td>47</td>
<td>17</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47</td>
<td>9</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>7</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>26</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>30</td>
<td>3</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Mucositis, oral</td>
<td>27</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>3</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fever</td>
<td>10</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>&lt;1</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Nose bleed</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Voice changes</td>
<td>29</td>
<td>&lt;1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>14</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Drug-related adverse reactions that resulted in treatment discontinuation were reported in 8.2% of regorafenib-treated patients compared with 1.2% of patients who received placebo

Common AEs occur early and stabilize over time

- Frequency of common AEs (all grades) decrease over time

CONCUR Trial Design
Regorafenib in Asian Patients

Asian patients with mCRC who progressed after standard therapies
25 Centers: mainland China, Hong Kong, South Korea, Taiwan, Vietnam

Regorafenib
160 mg daily
3 weeks on / 1 week off
(4-week cycle)
$n = 136$

- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

Placebo
$n = 68$

Primary endpoint: overall survival (OS)
- One-sided alpha 0.2 and assumed 33.3% OS improvement (HR=0.75 favoring regorafenib) with 154 events had 80% power

Secondary endpoints: progression-free survival, response rate, disease control rate

Li et al., WCGIC 2014
CONCUR: Progression-Free Survival (PFS)

Comparison using a stratified log-rank test (single vs multiple metastatic sites and ≥18 vs <18 months from mCRC diagnosis)

Li et al., WCGIC 2014
CONCUR: Overall Survival (OS)  
Primary Endpoint

Comparison using a stratified log-rank test (single vs multiple metastatic sites and ≥18 vs <18 months from mCRC diagnosis); one-sided alpha = 0.2

Events, n (%)  
Regorafenib (n=136)  
Placebo (n=68)  
95 (69.9)  
60 (88.2)

Median, months  
8.8  
6.3

HR [95% CI]  
0.550 [0.395–0.765]

P=0.0002 (1-sided)

45% reduction in risk of death in the regorafenib group

Li et al., WCGIC 2014
Session 7
Metastatic colorectal cancer II

The concept of drug reintroduction in late lines
The concept of drug reintroduction in late lines

• This is often done in practice
• But has never been really studied in clinical trials
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

Two lines of therapy 1 and 1' are similar. They have the same mechanism of action or consist of slightly different drug combinations.
Continuum of care in mCRC

• Continuum of care in mCRC is illustrated by the use of several « lines » of treatment:
  – Not always easy to determine
  – Possibly including surgery or loco-regional treatments
  – As well as single agent use of targeted therapy like anti-EGFR or Regorafenib

• This concept is associated with an improvement in overall survival