Metastatic Colorectal Cancer: Unanswered Questions in First Line Therapy

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Disclosures

Research Funding from Novartis, Sanofi, Taiho (Pending)
Agenda:

- Introduction

- Should the primary tumor be resected in metastatic colorectal cancer (mCRC)?

- What is the first line therapy of choice for mCRC: Bevacizumab (Bev) or EGFR monoclonal antibody (moAb)?

- Is there an optimal maintenance therapy regimen?
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Incidence & Mortality Trends

2014 Incidence (est) 138,830
2014 Mortality (est) 50,310

SEER Database
ACS Cancer Facts & Figures, 2013
Colon Cancer Staging

Stage at Diagnosis

- **Localized (Stage I/II):** 50%
- **Distant (Stage IV):** 20%
- **Regional (Stage III):** 30%

Figure 2. Colorectal Cancer Growth

© 2006 Teresa Winlow
Colon Cancer 5-year Survival by Stage

- All Stages: 65%
- Localized (Stage I and II): 70-90%
- Regional Stage III: 25-70%
- Distant (Stage IV): 5-10%
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• Is there an optimal maintenance therapy regimen?
Patients Rendered Disease-Free Overall Survival

<table>
<thead>
<tr>
<th>N (Events)</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>124 (34)</td>
<td>66.3 (59.8-NA)</td>
</tr>
</tbody>
</table>
Should Primary CRC Tumors Be Resected in Metastatic Disease?

- What are others doing?
  - 26,754 patients presented with stage IV colorectal cancer
  - 66% had primary tumor resected

Impact on survival of primary tumor resection in patients with colorectal cancer and unresectable metastasis

Pooled analysis of individual patients’ data from four randomized trials

M. Faron, A. Bourredjem, J.P. Pignon, O. Bouché, J.Y. Douillard, A. Adenis, D. Elias, M. Ducreux

Adapted from presentation by Faron et al, ASCO, 2012
Study Design

FFCD 9601
n = 294
- LV5FU2
- LV5FU2 (low dose leucovorin)
- Continuous 5FU
- Ralitrexed
- FOLFOX
- Bevacizumab + FOLFIRI
- Bevacizumab + XELIRI

FFCD 2000-05
n = 410
- LV5FU2
- FOLFOX
- FOLFIRI

ACCORD 13
n = 145
- Bevacizumab + FOLFIRI
- Bevacizumab + XELIRI

ML 16987
n = 306
- XELOX
- FOLFOX

Pooled Analysis of 810 mCRC patients
- Resection, n = 478 (59%)
- Intact Primary, n = 332 (41%)

Primary Endpoint: Overall Survival

Ducreux et al, JCO Vol 27, No 15S (May 20 Supplement), 2009: 4086
Int Journal of Cancer, 2011
### Forest plot

<table>
<thead>
<tr>
<th>Trial</th>
<th>Resection</th>
<th>No resection</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dead / Total</td>
<td>Dead / Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFCD 9601</td>
<td>130 / 146</td>
<td>60 / 60</td>
<td>0.5</td>
<td>[0.4, 0.7]</td>
</tr>
<tr>
<td>FFCD 2000-05</td>
<td>138 / 168</td>
<td>123 / 140</td>
<td>0.6</td>
<td>[0.4, 0.7]</td>
</tr>
<tr>
<td>ACCORD 13</td>
<td>24 / 59</td>
<td>24 / 37</td>
<td>0.6</td>
<td>[0.3, 1.1]</td>
</tr>
<tr>
<td>ML16987</td>
<td>58 / 105</td>
<td>74 / 95</td>
<td>0.6</td>
<td>[0.4, 0.8]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>350 / 478</td>
<td>281 / 332</td>
<td><strong>0.6</strong></td>
<td><strong>[0.5, 0.7]</strong></td>
</tr>
</tbody>
</table>

**Heterogeneity**  
\(p = 0.87\)

**Overall effect**  
\(p < 0.0001\)  
*Favors resection*  
*Favors no resection*
Limitations

• Retrospective studies – Selection bias?
• Modern chemo regimens not used

• NSABP C10: With 3-drug chemo, does intact primary still lead to unacceptable morbidity?
• Phase II trial of mFOLFOX6 + bev in 86 patients with metastatic colon ca, intact primary
• Estimated cumulative incidence of major morbidity related to intact primary at 24 mos is 16.3% (95%CI 7.6-25.1%) (10 surgeries, 2 deaths)

(McCahill et al, ASCO 2010, Abs# 3527)
The Role of Surgery of the Primary Tumour With Few or Absent Symptoms in Patients With Synchronous Unresectable Metastases of Colon Cancer (CAIRO4)

Patients with newly diagnosed metastatic colon cancer

- Randomized 1:1, phase III
- N = ~360 patients
- Primary endpoint: OS
- Secondary endpoints – PFS, RR, surgery related morbidity / mortality, QoL, Interval between randomization and systemic therapy, Patients requiring resection of primary in non-resection arm
- June 2012 – August 2015 in Netherlands

1st line rx with bev containing 3-drug regimen, surgery only if indicated

Upfront surgery followed by rx with bev containing 3-drug regimen

Rx beyond 1st line per physician

NCT01606098; PIs : Koopman, MD, Phd, Prof de Wilt
Should the primary tumor be resected in mCRC?

- Patients who are **asymptomatic** from the primary tumor at diagnosis do not need resection.

- A significant minority of patients will develop complications from the intact primary – close **surveillance** should be considered.

- **Pre-emptive** therapy when symptoms get worse preferred over emergent surgery.
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Studies of Cytotoxics for Advanced Colorectal Cancer
Tournigand Trial (GERCOR)

Randomized trial of 220 patients comparing the sequence of FOLFOX and FOLFIRI.

Untreated advanced colorectal cancer
(N=220)

Arm A: FOLFIRI -> FOLFOX

Arm B: FOLFOX -> FOLFIRI
1st line Chemotherapy: FOLFOX = FOLFIRI

Tournigand C et al. JCO 2004;22:229-237

©2004 by American Society of Clinical Oncology

P = .99

21.5 vs 20.6 mos
## 1st line FOLFIRI + biologic agent

<table>
<thead>
<tr>
<th></th>
<th>2107</th>
<th>CRYSTAL**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>IFL + / - Bev</td>
<td>FOLFIRI + / - cetux</td>
</tr>
<tr>
<td>ORR (%)*</td>
<td>45 vs 35</td>
<td>57 vs 40</td>
</tr>
<tr>
<td>p</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFS (m)*</td>
<td>10.6 vs 6.2</td>
<td>9.9 vs 8.4</td>
</tr>
<tr>
<td>HR / p</td>
<td>0.54 / &lt;0.001</td>
<td>0.69 / 0.0012</td>
</tr>
<tr>
<td>OS (m)*</td>
<td>20.3 vs 15.6</td>
<td>23.5 vs 20.0</td>
</tr>
<tr>
<td>HR / p</td>
<td>0.66 / &lt;0.001</td>
<td>0.79 / 0.009</td>
</tr>
</tbody>
</table>

* Experimental arm vs control arm

** KRAS exon 2 wt

# 1st line FOLFOX + biologic agent

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NO16966</th>
<th>OPUS**</th>
<th>COIN**</th>
<th>PRIME**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>FOLFOX / XELOX + / - bev</td>
<td>FOLFOX + / - cetux</td>
<td>FOLFOX / XELOX + / - cetux</td>
<td>FOLFOX + / - pmab</td>
</tr>
<tr>
<td>ORR (%)*</td>
<td>38 vs 38</td>
<td>57 vs 34</td>
<td>64 vs 57</td>
<td>55 vs 48</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>0.011</td>
<td>0.049</td>
<td>0.068</td>
</tr>
<tr>
<td>PFS (m)*</td>
<td>9.4 vs 8</td>
<td>8.3 vs 7.2</td>
<td>8.6 vs 8.6</td>
<td>9.8 vs 8</td>
</tr>
<tr>
<td>HR / p</td>
<td>0.83 / 0.0001</td>
<td>0.57 / 0.006</td>
<td>0.96 / NS</td>
<td>0.80 / 0.02</td>
</tr>
<tr>
<td>OS (m)*</td>
<td>21.3 vs 19.9</td>
<td>22.8 vs 18.5</td>
<td>17 vs 17.9</td>
<td>24 vs 20</td>
</tr>
<tr>
<td>HR / p</td>
<td>0.89 / NS</td>
<td>0.86 / NS</td>
<td>1.04 / NS</td>
<td>0.83 / 0.07</td>
</tr>
</tbody>
</table>

* Experimental arm vs control arm

KRAS exon 2 wt
CALGB/SWOG 80405: Phase III trial of FOLFIRI or FOLFOX with Bevacizumab or Cetuximab for patients w/ KRAS wild type untreated metastatic adenocarcinoma of the colon or rectum

A Venook, D Niedzwiecki, HJ Lenz, F Innocenti, M Mahoney, B O’Neil, J Shaw, B Polite, H Hochster, R Goldberg, R Mayer, R Schilsky, M Bertagnolli, C Blanke for the ALLIANCE and SWOG
CALGB/SWOG 80405: FINAL DESIGN

$mCRC$  
1st-line

$KRAS$ wild type  
(codons 12,13)

$STRATA$:  
FOLFOX/FOLFIRI  
Prior adjuvant  
Prior XRT

FOLFIRI or FOLFOX  
MD choice

Chemo + Cetuximab

Chemo + Bevacizumab

$N = 1140$

1° Endpoint: Overall Survival

2° Endpoints: PFS, chemo / biologic agent interaction
CALGB/SWOG 80405: Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>OS (m)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Cetux</td>
<td>578 (375)</td>
<td>29.9</td>
<td>27.0-32.9</td>
</tr>
<tr>
<td>Chemo + Bev</td>
<td>559 (371)</td>
<td>29.0</td>
<td>25.7-31.2</td>
</tr>
</tbody>
</table>

P=0.34
HR 0.925 (0.78-1.09)
CALGB/SWOG 80405: Progression-Free Survival (Investigator Determined)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>PFS (m)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Bev</td>
<td>559 (498)</td>
<td>10.8</td>
<td>9.7-11.4</td>
</tr>
<tr>
<td>Chemo + Cetux</td>
<td>578 (499)</td>
<td>10.4</td>
<td>9.6-11.3</td>
</tr>
</tbody>
</table>

P=0.55
HR 1.04 (0.91 -1.17)
CALGB/SWOG 80405: Overall Survival
FOLFOX vs FOLFIRI Treated

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>OS (m) Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX + Cetux</td>
<td>426 (277)</td>
<td>30.1</td>
<td>26.6-34.8</td>
</tr>
<tr>
<td>FOLFOX + Bev</td>
<td>409 (290)</td>
<td>26.9</td>
<td>24.7-30.0</td>
</tr>
</tbody>
</table>

P=0.09 HR 0.9 (0.7-1.0)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>OS (m) Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI + Bev</td>
<td>150 (81)</td>
<td>33.4</td>
<td>27.3-41.3</td>
</tr>
<tr>
<td>FOLFIRI + Cetux</td>
<td>152 (98)</td>
<td>28.9</td>
<td>25.6-34.2</td>
</tr>
</tbody>
</table>

P=0.28 HR 1.2 (0.9-1.6)
EORTC GLOBAL QOL

DSQL SKIN SATISFACTION

---

BEVACIZUMAB

CETUXIMAB

Score (0-100 scale, Higher scores represent better QOL)

Baseline  Week 6  Month 3  Month 6  Month 9  Baseline  Week 6  Month 3  Month 6  Month 9

P = 0.0546

P < 0.0001

Slide courtesy of Dueck, Schrag, Naughton
CALGB/SWOG 80405: Conclusions

• Overall survival on Chemo/Cetuximab is no different than on Chemo/Bevacizumab in 1st line treatment for patients with KRAS wild type (codons 12 & 13) metastatic colorectal cancer

• FOLFIRI or FOLFOX w/ either Bevacizumab or Cetuximab can be considered options for 1st line therapy of patients with KRAS wt metastatic CRC
<table>
<thead>
<tr>
<th></th>
<th>PEAK*</th>
<th>FIRE3*</th>
<th>CALGB80405*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>FOLFOX + pmab vs FOLFOX + bev</td>
<td>FOLFIRI + cetux vs FOLFIRI + bev</td>
<td>chemo + cetux vs chemo + bev</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>58 vs 54</td>
<td>62 vs 58</td>
<td>Pending</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>0.183</td>
<td></td>
</tr>
<tr>
<td>PFS (m)*</td>
<td>10.9 vs 10.1</td>
<td>10 vs 10.3</td>
<td>10.4 vs 10.8</td>
</tr>
<tr>
<td>HR / p</td>
<td>0.87 / 0.35</td>
<td>1.06 / 0.547</td>
<td>1.04 / 0.55</td>
</tr>
<tr>
<td>OS (m)*</td>
<td>52 vs 37</td>
<td>28.7 vs 25</td>
<td>29.9 vs 29</td>
</tr>
<tr>
<td>HR / p</td>
<td>0.62 / 0.009</td>
<td>0.77 / 0.017</td>
<td>0.34 / 0.925</td>
</tr>
</tbody>
</table>


* KRAS exon 2 wt
Expanded RAS analysis

- **KRAS**
  - exon 2 mt, 35%
- **RAS wt**, 50%
- **New RAS mt**, 15%

Tabernero, ASCO 2014
Expanded RAS analysis : EGFR MoAb vs Bev in 1st line

chemo + EGFR MoAb vs chemo + bev

<table>
<thead>
<tr>
<th></th>
<th>KRAS exon 2 wt</th>
<th>Expanded RAS wt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>57.8 vs 53.5</td>
<td>63.6 vs 60.5</td>
</tr>
<tr>
<td>FIRE3</td>
<td>62 vs 58</td>
<td>61 vs 59.4</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>10.9 vs 10.1</td>
<td>13 vs 9.5 (p = 0.029; HR 0.44 – 0.96)</td>
</tr>
<tr>
<td>FIRE3</td>
<td>10 vs 10.3</td>
<td>9.9 vs 10.3</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>34.2 vs 24.3 (p = 0.009; HR 0.44 – 0.89)</td>
<td>41.3 vs 28.9 (p = 0.058; HR 0.39 – 1.02)</td>
</tr>
<tr>
<td>FIRE3</td>
<td>28.7 vs 25 (p = 0.017; HR 0.62 – 0.96)</td>
<td>33.1 vs 25.6 (p = 0.011; HR 0.53 – 0.92)</td>
</tr>
</tbody>
</table>

Benefit with expanded RAS validated in multiple studies : OPUS, CRYSTAL, PRIME

Schwartzberg JCO 2014, Falcone ASCO 2013
Peri-Operative FOLFOX for Resectable Hepatic Metastases

EORTC 40983

- n = 364, resectable liver metastases*
- Primary endpoint: disease free survival

*1-4 metastases: 52% one, 26% two, 15% three, 7% four mets
56% colon CA, 42% rectal CA; enrolled 2000-2004
No prior oxaliplatin allowed

FOLFOX4 6 cycles (3m) → Surgery → FOLFOX4 6 cycles (3m)

~4 weeks

Nordlinger et al, Lancet 2008,
Adapted from Messersmith, Great Debates and Updates in GI Malignancies, 2009
## Final Results of EORTC 40983

<table>
<thead>
<tr>
<th></th>
<th>No. Pts CT</th>
<th>No. Pts Surgery</th>
<th>Absolute Difference in 3-Year PFS (95.66% Confidence Interval)</th>
<th>Absolute Difference in 5-year and median overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (ITT)</td>
<td>182</td>
<td>182</td>
<td>+7.3% (28.1%–35.4%) HR 0.79 (0.62–1.02) p = 0.058</td>
<td>+3.4% at 5 years; +7 months in median OS HR 0.88 (0.68–1.14) p = 0.339</td>
</tr>
<tr>
<td>All eligible patients</td>
<td>171</td>
<td>171</td>
<td>+8.1% (28.1%–36.2%) HR 0.77 (0.6–1.00) p = 0.041</td>
<td>+4.1% at 5 years; +8.7 months in median OS HR 0.87 (0.66–1.14) p = 0.303</td>
</tr>
</tbody>
</table>

* Median follow-up 8.5 years

Courtesy of Dr. B. Nordlinger.
Presented By John Neil Primrose, MD, FRCS at 2013 ASCO Annual Meeting

Primary Endpoint: PFS

**KRAS WT**

Operable (including borderline operable) colorectal liver metastases

- Arm A (control)
  - Chemotherapy 12 weeks
  - Liver resection
  - Chemotherapy 12 weeks

- Arm B (experimental)
  - Chemotherapy + cetuximab 12 weeks
  - Liver resection
  - Chemotherapy + cetuximab 12 weeks
Primary analysis

Progression free survival of all randomised KRAS wild type patients
The median PFS was 20.5 months Arm A vs 14.1 months Arm B
Chemotherapy Associated Steatohepatitis (CASH)

Normal Liver

Steatohepatitis: Fatty vesicles
EtOH, NASH
CASH:
5-FU (40-47%)
Irinotecan (Increased further)

Sinusoidal Obstruction Syndrome
Obstruction of sinusoids by fibrosis
RBC -> congestion
(Oxali) Platin (49-78%)

Kneuertz et al, Annals of Surgical Oncology 2010
Optimal Duration of Neoadjuvant Chemotherapy

Influence of Number of Cycles of Pre-Op Chemo on Morbidity

45 with neoadjuvant chemo vs 22 without

No change in mortality

Pre-op chemo associated with:
- Increased hepatic injury (49% vs 25% p = 0.005)
- Increase morbidity (38% vs 13.5%, p = 0.03)

Karoui, Ann Surg 2006

Adapted from Messersmith Great Debates and Updates in GI Malignancies, 2009
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• Should the primary tumor be resected in metastatic colorectal cancer (mCRC)?

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• Is there an optimal maintenance therapy regimen?
OPTIMOX Studies: Maintenance or Treatment Holiday

OPTIMOX1\(^1\)
Maintenance therapy
(n = 620)

- FOLFOX 4 until progression
- FOLFOX 7
- sLV5FU2

OPTIMOX2\(^2\)
Chemotherapy-free interval
(n = 202)

- mFOLFOX 7
- sLV5FU2
- mFOLFOX 7
- mFOLFOX 7

Chemotherapy-Free Interval

OPTIMOX Studies: Results

• OPTIMOX1 (maintenance vs continuous therapy)
  • No significant difference in duration of disease control, PFS, or OS

• OPTIMOX2 (treatment holiday vs maintenance therapy)
  • Significantly better duration of disease control and PFS with maintenance therapy
  • No significant difference in OS

Maintenance Bevacizumab: MACRO Trial

Patients with newly diagnosed mCRC and ECOG PS ≤ 2

Capecitabine + Oxaliplatin + Bevacizumab x 6 cycles q3w (n = 241)

Capecitabine + Oxaliplatin + Bevacizumab
Capecitabine + Oxaliplatin + Bevacizumab until progression

Bevacizumab until progression

MACRO: Overall Survival (ITT)

<table>
<thead>
<tr>
<th></th>
<th>XELOX-Bev</th>
<th>Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>239</td>
<td>241</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>175 (73)</td>
<td>174 (7%)</td>
</tr>
<tr>
<td>Censored, n (%)</td>
<td>64 (27)</td>
<td>67 (28)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>23.2 (19.79,-26.01)</td>
<td>19.99 (17.98-23.25)</td>
</tr>
<tr>
<td>HR:</td>
<td>1.05 (95% CI: 0.851-1.295)</td>
<td></td>
</tr>
</tbody>
</table>

AIO 0207: Treatment algorithms

**Induction:** 24 wks

- FP* + Bev + Oxaliplatin
  - with CR/PR/SD

**Maintenance:** non-PD

- FP* + Bev
- Bev
- no treatment

**Re-Induction**

- any FP* +/- Bev +/- Ox

**Stratification**
- Adjuvant tx.
- CR/PR vs. SD
- ECOG PS
- CEA @ baseline

**Primary End Point**

- PFS1
- TFS

*FP* = any fluoropyrimidine in a standard protocol (e.g. mFOLFOX6, FOLFOX4, Cape/Ox, LV5FU2; Cape 2x1000)

Bev used in standard doses (5mg/kg q 2 wks or 7.5mg/kg q 3wks arm A; 7.5 mg/kg 3q 3 wks arm B)

Presented by: Dirk Arnold, on behalf of the AIO CRC study group
TFS: All arms

- **FP/Bev:** n=141, 115 events, median = 6.8 months
- **Bev:** n=153, 129 events, median = 6.5 months
- **No therapy:** n=153, 138 events, median = 6.1 months

Median TFS all patients: 6.5 months (from randomization)

Log rank test: p=0.099

Presented by: Dirk Arnold, on behalf of the AIO CRC study group
PFS1 from start of maintenance

- **FP/Bev**: n=141, 116 events, median = 6.2 months
- **Bev**: n=153, 135 events, median = 4.8 months
- **No therapy**: n=153, 145 events, median = 3.6 months

Med. PFS1 all patients from rand.: 4.6 months

B vs A: HR=1.21; 95% CI: 0.95-1.56; log rank p=0.13
C vs A: HR=2.06; 95% CI: 1.60-2.66; log rank p<0.001
C vs B: HR=1.57; 95% CI: 1.24-1.99; log rank p<0.001
Log rank test: p<0.0001

Presented by: Dirk Arnold, on behalf of the AIO CRC study group
Re-induction rates and PFS1/TFS

Presented by: Dirk Arnold, on behalf of the AIO CRC study group
OS from start of maintenance

- **FP/bev**: n=157, 70 events, median = 23.8 months
- **Bev**: n=156, 67 events, median = 26.2 months
- **No therapy**: n=156, 66 events, median = 23.1 months

Median OS all patients: 23.7 months (from randomization)

N=473
Interim analysis: 203 events
Log rank p=0.70

Presented by: Dirk Arnold, on behalf of the AIO CRC study group
Maintenance treatment with capecitabine + bevacizumab versus observation after induction treatment with chemotherapy + bevacizumab in metastatic colorectal cancer

Final results and subgroup analyses of the phase 3 CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG)

ASCO June 2\textsuperscript{nd} 2014, Chicago

Study design

SD or better after 6 cycles CAPOX-B

• Stratification factors: prior adjuvant therapy, serum LDH, response to induction treatment, WHO PS, institution
• Primary endpoint: PFS2
• PFS2 is considered to be equal to PFS1 for patients in whom CAPOX-B is not reintroduced after PFS1 for any reason

observation

capecitabine + bevacizumab

re-introduction CAPOX-B

PD

PFS1

PFS2
Primary endpoint PFS2

Median PFS2

- **Observation**: 8.5 m [95%CI: 7.4-10.4]
- **Maintenance**: 11.7 m [95%CI: 10.1-13.3]
- **Stratified HR**: 0.67 [95%CI: 0.56-0.81]
- **p value**: <0.0001
- **adjusted HR**: 0.64 [95%CI: 0.53-0.76]

- Induction treatment of 6x cycles CAPOX-B prior to randomization not included (4-5 m)
- PFS2 = PFS1 for pts in whom CAPOX-B is not reintroduced after PFS1 for any reason
PFS1

Median PFS1
- Observation: 4.1 m [95%CI: 3.9-4.2]
- Maintenance: 8.5 m [95%CI: 6.5-10.3]
Stratified HR: 0.43 [95%CI: 0.36-0.52]
$p$ value: < 0.0001

adjusted HR: 0.39 [95%CI: 0.33-0.48]

Induction treatment of 6x cycles CAPOX-B prior to randomization not included (4-5 m)
Overall Survival

Median OS
- Observation: 18.1 m [95%CI: 16.3-20.2]
- Maintenance: 21.6 m [95%CI: 19.4-23.8]
- Stratified HR: 0.89 [95%CI: 0.73-1.07]
- p value: 0.22

Adjusted HR: 0.83 [95%CI: 0.68-1.01]

Median OS from start induction treatment prior to randomization
- Observation: 22.4 m [95% CI 20.8-24.9]
- Maintenance: 25.9 m [95% CI 23.7-28.4]
CAIRO3 Quality of life during maintenance/observation

- QoL was maintained during maintenance treatment, and was clinically not inferior compared to QoL in observation arm.

Between-group difference: 3.9 (95%CI 1.2; 6.5) p=0.004 (not clinically relevant, < 10)
Maintenance trials: Combined analysis, vs. no tx.

Koopman et al., GI Cancer Symposium 2014; abstract LBA388;
Köberle et al., ASCO 2013 J Clin Oncol 31, 2013 (suppl.); abstr. 3503
Maintenance therapy in colon cancer

1st line induction chemotherapy (FOLFOX + bev)

- Resectable (10%)
  - Surgery

- Progression (10-15%)

2nd line therapies

Response / stable (70-80%)

One size doesn’t fit all!
Consider multiple factors:
- Clinical scenario,
- Patient preference,
- Toxicities
- Costs etc

If continued response,
continue FOLFOX + bev

If stable disease,
maintenance therapy, 5-FU + bev

If low volume, consider treatment break
Thank you for your attention!

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