Abstract Discussion Session:
Selecting the optimal first line treatment in advanced colorectal cancer

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London and Surrey, UK
Disclosure

- Research funding: 4SC, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Clovis, Eli Lilly, Janssen, Medimmune, Merck, Merrimack
O-022  Phase II study evaluating trifluridine/tipiracil+bevacizumab and capecitabine+bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): results of the primary analysis  

Eric Van Cutsem

O-023  FOLFOX/Bevacizumab +/- Irinotecan in advanced colorectal cancer (CHARTA): long term outcome  

Hans-Joachim Schmoll

O-024  mFOLFOXIRI + Panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild-type metastatic colorectal cancer (mCRC): a randomized phase II VOLFI trial of the AIO (AIO- KRK0109)  

Michael Geissler
ESMO algorithm for 1st line treatment of mCRC

Assessment of clinical condition of the patient

- F1
- Unfit (but may be suitable)
- Unfit

GOAL

Patients with clearly resectable metastases
- Surgery alone
- Surgery with perioperative postoperative CT

Cytoreduction (Shrinkage)**

OMD See figure 2

MOLECULAR PROFILE

- RAS wt
- RAS mt
- BRAF mt

CT doublet + anti-EGFR
Combination CT + bevacizumab
CT triplet + bevacizumab
CT doublet + biological agent
CT doublet + bevacizumab
CT triplet + bevacizumab

Re-evaluation/assessment of response every 2 months*

Second-line

Disease control (control of progression)

- RAS wt
- RAS mt
- BRAF mt

CT doublet + bevacizumab
CT triplet + bevacizumab
CT doublet + bevacizumab
CT triplet + bevacizumab

Re-evaluation/assessment of response every 2–3 months*

Surgery

Disease control

- Progression: Continue; maintenance; or pause
- Progression: Second-line

Cytoreduction (Shrinkage)**

Second-line

Continue

Pan-Asian adapted ESMO algorithm for 1st line treatment of mCRC

ASSESSMENT OF CLINICAL CONDITION OF THE PATIENT

Fit
GOAL

Unfit (but may be suitable)

FP + anti-EGFR; FP + bevacizumab; reduced
dose CT doublet; anti-EGFR

Unfit

BSC

Patients with clearly resectable metastases

Surgery alone; surgery with perioperative/
postoperative CT

OMD Cytoreduction (Shrinkage)*

MOLECULAR PROFILE

RAS wt

RAS mt

BRAF mt

Left sided:
CT doublet* + anti-EGFR
Right sided:
CT triple/doublet* + bevacizumab

Combination CT +
bevacizumab

CT triplet +
bevacizumab

Left sided:
CT doublet* + anti-EGFR
Right sided:
CT doublet +
bevacizumab

CT doublet +
bevacizumab

CT triplet +
bevacizumab

Disease control (Control of progression)

MOLECULAR PROFILE

Re-evaluation/assessment of response every 2 months**

GOAL

Progressive disease

Surgery

Cytoreduction (Shrinkage)**

Disease control

Continue

Continue; maintenance; or pause

Second-line

Progressive disease

Second-line

2017 Pan-Asian adapted ESMO consensus guidelines – Yoshino, Ann Oncol 2018
Pan-Asian adapted ESMO algorithm for 1st line treatment of mCRC

ASSESSMENT OF CLINICAL CONDITION OF THE PATIENT

Fit\textsuperscript{b} GOAL

Fit\textsuperscript{b} (but may be suitable)

OMD Cytoreduction (Shrinkage)*

Unfit\textsuperscript{b} MOLECULAR PROFILE

Disease control (Control of progression)

Unfit\textsuperscript{b}

BSC

Patients with clearly resectable metastases

Surgery

Survived or postoperatively

RAS wt

Left sided:
CT doublet\textsuperscript{c} + anti-EGFR
Right sided:
CT doublet\textsuperscript{c} + bevacizumab

Second-line

\textsuperscript{a} Continue or palliative care

\textsuperscript{b} Not fit for chemotherapy and bevacizumab

FP + anti-EGFR, FP + bevacizumab; reduced dose CT doublet; anti-EGFR

2017 Pan-Asian adapted ESMO consensus guidelines – Yoshino, Ann Oncol 2018
| O-022 | Phase II study evaluating trifluridine/tipiracil+bevacizumab and capecitabine+bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): results of the primary analysis | Eric Van Cutsem |
| O-023 | FOLFOX/Bevacizumab +/- Irinotecan in advanced colorectal cancer (CHARTA): long term outcome | Hans-Joachim Schmoll |
| O-024 | mFOLFOXIRI + Panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild-type metastatic colorectal cancer m(CRC): a randomized phase II VOLFI trial of the AIO (AIO- KRK0109) | Michael Geissler |
Trifluridine is a nucleoside analogue which inhibits TS and is also integrated into DNA. Tipiracil hydrochloride inhibits thymidine phosphorylase which degrades trifluridine.
Trifluridine/Tipiracil (TT) in GI Cancer

- TT significantly improves survival in chemotherapy refractory metastatic CRC from 5.2 to 7.2 months (HR 0.69)
- TT significantly prolongs survival in chemotherapy refractory gastric cancer from 3.6 to 5.7 months (HR 0.57)
- **What is its role in the earlier treatment in metastatic CRC?**
Bevacizumab with single agent capecitabine in elderly patients

- **AVEX Study**
  - 1st line Capecitabine ± Bev
  - n = 280 mCRC pts ≥70 yrs
  - Primary endpoint: PFS

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab plus capecitabine group (n=140)</th>
<th>Capecitabine group (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>76 (70-87)</td>
<td>77 (70-87)</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>55 (39%)</td>
<td>46 (33%)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>85 (61%)</td>
<td>94 (67%)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>70 (50%)</td>
<td>60 (43%)</td>
</tr>
<tr>
<td>1</td>
<td>58 (41%)</td>
<td>67 (48%)</td>
</tr>
<tr>
<td>2</td>
<td>10 (7%)</td>
<td>11 (8%)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Missing data</strong></td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>History of medical condition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>79 (56%)</td>
<td>68 (49%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9 (6%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>10 (7%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>8 (6%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Chronic gastrointestinal inflammation</td>
<td>4 (3%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Use of any concomitant drugs</strong></td>
<td>129 (92%)</td>
<td>127 (91%)</td>
</tr>
</tbody>
</table>

**Key inclusion criteria**
- ECOG PS 0–2
- Not optimal candidates for a combination chemotherapy with irinotecan or oxaliplatin

**Key exclusion criteria**
- Clinically significant cardiovascular disease
Capecitabine plus bevacizumab is an effective and well tolerated regimen

**Median Progression-free survival**
- Capecitabine alone: 5.1 m
- Capecitabine + Bevacizumab: 9.1 m

HR 0.53 (95% CI 0.41-0.69)
*p* < 0.0001

≥G3 treatment-related AEs similar in 2 groups (except thromboembolic events and hand-foot syndrome)
Design of the TASCO1 trial

Phase II

mCRC untreated, ECOG 0-2
Non-eligible for intensive therapy

Stratification:
RAS status, ECOG PS, Country

Randomised 1:1

TT – B
Trifluridine/Tipiracil
35 mg/m² b.i.d. p.o. d1-5, 8-12 q4wks
+ Bevacizumab
5mg/kg IV d1, d15 q4wks (N=77)

C-B
Capecitabine
1250 or 1000 mg/m² b.i.d. p.o. d1-14 q3wks
+ Bevacizumab
7.5mg/kg IV d1 q3wks (N=76)

Primary Endpoint:
• Progression free survival (PFS)

Secondary Endpoints:
Overall Response Rate (ORR), Duration of Response (DR), Disease control rate (DCR), Overall Survival (OS), Safety and tolerability and QoL
TASCO1 trial: PFS

- **Primary endpoint:** Non-significant trend in improvement in PFS with TT-B vs C-B
- This effect was consistent across most subgroups
- OS data not yet mature although trend in efficacy
- C-B PFS 7.8m versus 9.1m in AVEX

* Hazard ratio adjusted on stratification covariates
**TASCO1 trial: PFS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>P-value interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS status</td>
<td>Mutant</td>
<td>0.900</td>
<td>0.900</td>
<td>0.900</td>
</tr>
<tr>
<td></td>
<td>Wild</td>
<td>0.900</td>
<td>0.900</td>
<td>0.900</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0</td>
<td>0.508</td>
<td>0.508</td>
<td>0.508</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.682</td>
<td>0.682</td>
<td>0.682</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.682</td>
<td>0.682</td>
<td>0.682</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>0.163</td>
<td>0.163</td>
<td>0.163</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.163</td>
<td>0.163</td>
<td>0.163</td>
</tr>
<tr>
<td>Age</td>
<td>≤65</td>
<td>0.017</td>
<td>0.017</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>0.666</td>
<td>0.666</td>
<td>0.666</td>
</tr>
<tr>
<td>Age 65</td>
<td>≤65</td>
<td>0.702</td>
<td>0.702</td>
<td>0.702</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>0.577</td>
<td>0.577</td>
<td>0.577</td>
</tr>
<tr>
<td>Age 75</td>
<td>≤75</td>
<td>0.403</td>
<td>0.403</td>
<td>0.403</td>
</tr>
<tr>
<td></td>
<td>&gt;75</td>
<td>0.577</td>
<td>0.577</td>
<td>0.577</td>
</tr>
<tr>
<td>Region</td>
<td>Europe</td>
<td>0.763</td>
<td>0.763</td>
<td>0.763</td>
</tr>
<tr>
<td></td>
<td>Outside Europe</td>
<td>0.659</td>
<td>0.659</td>
<td>0.659</td>
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<tr>
<td>Prior adjuvant treatment</td>
<td>No</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.763</td>
<td>0.763</td>
<td>0.763</td>
</tr>
<tr>
<td>Primary tumour site</td>
<td>Left colon</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Right colon</td>
<td>0.197</td>
<td>0.197</td>
<td>0.197</td>
</tr>
<tr>
<td>Surgery resection</td>
<td>No</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.935</td>
<td>0.935</td>
<td>0.935</td>
</tr>
<tr>
<td>Number of met sites</td>
<td>≤3</td>
<td>0.187</td>
<td>0.187</td>
<td>0.187</td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>0.482</td>
<td>0.482</td>
<td>0.482</td>
</tr>
<tr>
<td>Presence of liver met</td>
<td>No</td>
<td>0.120</td>
<td>0.120</td>
<td>0.120</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.544</td>
<td>0.544</td>
<td>0.544</td>
</tr>
<tr>
<td>BRAF status</td>
<td>Mutant</td>
<td>0.347</td>
<td>0.347</td>
<td>0.347</td>
</tr>
<tr>
<td></td>
<td>Not done</td>
<td>0.531</td>
<td>0.531</td>
<td>0.531</td>
</tr>
<tr>
<td>Time since met diagnosis</td>
<td>≤4</td>
<td>0.104</td>
<td>0.104</td>
<td>0.104</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>0.740</td>
<td>0.740</td>
<td>0.740</td>
</tr>
</tbody>
</table>

* Hazard ratio adjusted on stratification covariates

- **Primary endpoint**: Non-significant trend in improvement in PFS with TT-B vs C-B
- This effect was consistent across most subgroups
- OS data not yet mature although trend in efficacy
- C-B PFS 7.8m versus 9.1m in AVEX
## TASCO1 trial: PFS multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Levels</th>
<th>P value*</th>
<th>Hazard ratio**</th>
<th>95% CI** [Low, High]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>TT-B vs. C-B</td>
<td>0.0355</td>
<td>0.64</td>
<td>[0.42, 0.97]</td>
</tr>
<tr>
<td>RAS Status (strat.)</td>
<td>WT vs. MT</td>
<td>0.1923</td>
<td>0.74</td>
<td>[0.47, 1.17]</td>
</tr>
<tr>
<td>ECOG (strat.)</td>
<td>0 vs. 1</td>
<td>0.0010</td>
<td>0.43</td>
<td>[0.26, 0.71]</td>
</tr>
<tr>
<td></td>
<td>1 vs. 2</td>
<td>0.2017</td>
<td>0.70</td>
<td>[0.41, 1.21]</td>
</tr>
<tr>
<td>Gender</td>
<td>Male vs. female</td>
<td>0.0212</td>
<td>0.60</td>
<td>[0.39, 0.93]</td>
</tr>
<tr>
<td>Presence of liver metastasis</td>
<td>Y vs. N</td>
<td>0.0600</td>
<td>1.58</td>
<td>[0.98, 2.53]</td>
</tr>
<tr>
<td>BRAF status</td>
<td>WT vs. MT</td>
<td>0.0656</td>
<td>0.49</td>
<td>[0.23, 1.05]</td>
</tr>
<tr>
<td></td>
<td>Not done vs. MT</td>
<td>0.5906</td>
<td>0.80</td>
<td>[0.34, 1.83]</td>
</tr>
<tr>
<td>Neutrophil-Lymphocyte Ratio (NLR)</td>
<td>&lt;3 vs. ≥ 3</td>
<td>0.1760</td>
<td>0.75</td>
<td>[0.50, 1.14]</td>
</tr>
</tbody>
</table>

*Wald Chi-Square Test

**Hazard Ratio of arm 1 (relative to arm 2) from Cox Regression including terms for all factors shown
# TASCO1 trial: adverse events

<table>
<thead>
<tr>
<th></th>
<th>TT-B</th>
<th>C-B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any SE (%)</strong></td>
<td>54.5</td>
<td>57.9</td>
</tr>
<tr>
<td>All grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non- haematological (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>53.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>46.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Reduced appetite</td>
<td>37.7</td>
<td>-</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>3.9</td>
<td>-</td>
</tr>
<tr>
<td><strong>Haematological (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>31.2</td>
<td>9.1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>53.2</td>
<td>22.1</td>
</tr>
<tr>
<td>N count decrease</td>
<td>23.4</td>
<td>14.3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Serious febrile neutropenia</td>
<td>3.9</td>
<td></td>
</tr>
</tbody>
</table>
ESMO algorithm for 1st line treatment of mCRC in 2018

TASCO1 Trial

- Trifluridine/Tipiracil with bevacizumab appears to be a promising alternative first line treatment to capecitabine and bevacizumab in patients unsuitable for doublet chemotherapy but with a different side effect profile

- A confirmatory Phase 3 trial would be desirable
**Proffered abstracts**

O-022  Phase II study evaluating trifluridine/tipiracil+bevacizumab and capecitabine+bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): results of the primary analysis  

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Michael Geissler
### Randomised trials of triplet chemotherapy plus bevacizumab

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>n</th>
<th>Treatment arms</th>
<th>mPFS (p value)</th>
<th>mOS (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIBE</td>
<td>1st line</td>
<td>508</td>
<td>FOLFOXIRI-Bev vs FOLFIRI-Bev</td>
<td>12.1 vs 9.7</td>
<td>29.8 vs 25.8</td>
</tr>
<tr>
<td>Loupakis, 2014</td>
<td></td>
<td></td>
<td>5FU-Bev</td>
<td>(p=0.003)</td>
<td>(p=0.03)</td>
</tr>
<tr>
<td>OLIVIA</td>
<td>1st line (unresectable liver only disease)</td>
<td>80</td>
<td>FOLFOXIRI-Bev vs FOLFOX-Bev</td>
<td>18.6 vs 11.5</td>
<td>NR vs 32.2</td>
</tr>
<tr>
<td>Gruenberger, 2014</td>
<td></td>
<td></td>
<td>NA</td>
<td>(not reported)</td>
<td>(not reported)</td>
</tr>
<tr>
<td>STEAM</td>
<td>1st line</td>
<td>280</td>
<td>cFOLFOXIRI-Bev vs sFOLFOXIRI-Bev vs FOLFOX-Bev</td>
<td>11.86 vs 11.37 vs 9.46</td>
<td>34 vs 28 vs 31</td>
</tr>
<tr>
<td>Hurwitz, 2017</td>
<td></td>
<td></td>
<td>5FU –Bev or Capecitabine-Bev</td>
<td>(p=0.01)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CHARTA</td>
<td>1st line</td>
<td>250</td>
<td>FOLFOXIRI-Bev vs FOLFOX-Bev</td>
<td>12 vs 10.3</td>
<td>28 vs 24</td>
</tr>
<tr>
<td>Schmoll, 2018</td>
<td></td>
<td></td>
<td>5FU-Bev or Capecitabine-Bev</td>
<td>(p=0.19)</td>
<td>(p=0.21)</td>
</tr>
</tbody>
</table>
TRIBE: Dose intensifying chemotherapy across molecular subtypes and tumour sidedness

Overall survival

- Treatment effect on OS not significantly different across molecular subtypes
- BRAF-mt OS 19 vs 10.7m, HR 0.54 [0.24-1.20]) and sample size small (n =28)
- However, intensive 1st line FOLFOXIRI+Bev regimen may be considered in poor prognosis BRAF mutant patients
- Dose intensifying chemotherapy improves outcome in right sided colon cancer
Design of the CHARTA trial

**Primary Endpoint:**
- Progression free survival (PFS) at 9m

**Secondary Endpoints:**
Response rate (RR), progression free survival (PFS), overall survival (OS), secondary resection rate, tolerability, QoL

mCRC untreated, ECOG 0-2

Stratified: ESMO groups 1,2,3

Randomised 1:1

Induction 6 months

A: FOLFOX + Bev

B: FOLFOXIRI + Bev

Capecitabine + Bev

Maintenance

Until PD or 12m

Schmoll, ESMO GI 2018
CHARTA trial – Results

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX-B</th>
<th>FOLFOXIRI-B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (9m)</td>
<td>57%</td>
<td>68%</td>
<td>p=0.085</td>
</tr>
<tr>
<td>PFS (mos)*</td>
<td>10.3</td>
<td>12</td>
<td>p = 0.19</td>
</tr>
<tr>
<td>OS (mos)*</td>
<td>24</td>
<td>28</td>
<td>p= 0.21</td>
</tr>
</tbody>
</table>

Secondary resection

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>21%</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>11.5</td>
</tr>
<tr>
<td>OS (mos)</td>
<td>45.3</td>
</tr>
</tbody>
</table>

* Updated results

- Largest subgroup of synchronous metastases (n=211, 91%) PFS significantly improved from 10.1 to 11.8 months p=0.023
- FOLFOXIRI-Bev did not significantly improve outcomes in BRAFmt (n=13)
- 4-drug combination showed tolerable toxicities
Subgroup analysis: CHARTA trial

Synchronous

- A: 22.51
- B: 27.96
HR 0.74
p = 0.054

Metachronous

- A: 29.31
- B: 27.76
HR 1
p = 0.99

Synchronous, resection of primary

- A: 30.65
- B: 30.46
HR 0.84
95% CI: 0.53 - 1.3
p = 0.48

Synchronous, no resection of primary

- A: 17.02
- B: 26.45
HR 0.64
95% CI: 0.42 - 0.96
p = 0.028
The CHARTA trial

- No significant improvement in overall PFS or survival but the trial was probably underpowered
- Subgroup analysis shows improved OS with synchronous metastases associated with an unresected primary and it is postulated this group may benefit most from triplet chemotherapy but needs confirmation
| O-022 | Phase II study evaluating trifluridine/tipiracil+bevacizumab and capecitabine+bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): results of the primary analysis | Eric Van Cutsem |
| O-023 | FOLFOX/Bevacizumab +/- Irinotecan in advanced colorectal cancer (CHARTA): long term outcome | Hans-Joachim Schmoll |
| O-024 | mFOLFOXIRI + Panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild-type metastatic colorectal cancer m(CRC): a randomized phase II VOLFI trial of the AIO (AIO- KRK0109) | Michael Geissler |
Design of the VOLFI trial

**mCRC**
- Unresectable
- 1st-line
- WT RAS**
- Age ≥ 18yrs
- ECOG PS 0-1

N = 96

**Randomization:** 2:1

- **mFOLFOXIRI + panitumumab 6 mg/kg**
  - Q2W
  - N = 63

- **FOLFOXIRI Q2W**
  - N = 33

**Treatment until PD, resectability or to a maximum 12 cycles**

**Strata:**
- Cohort 1: definitely inoperable or unresectable
- Cohort 2: chance of secondary resection with curative intent

**Primary Endpoint:**
- Objective response rate (ORR)

**Secondary Endpoints:**
- PFS, OS, DCR, duration of response, QoL (QLQ-C30), secondary resection rate of metastases, pathological response and liver toxicity (cohort 2) and toxicity

**amendment in 11/2013 to include all RAS wild-type only**
In this study the primary endpoint was met and the response rate to FOLFOXIRI was increased by the addition of panitumumab from 60.6 to 87.3%, p= 0.004

Interestingly in BRAF mt tumours which are typically regarded as being resistant to EGFR inhibitors the response rate was increased from 22.2 to 85.7% but the total number of patients is small n=16
Progression free survival (PFS): VOLFI

**PFS by treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events n (%)</th>
<th>Median months (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOXIRI-P</td>
<td>54 (85.7)</td>
<td>9.7 (9.0-11.7)</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>29 (87.9)</td>
<td>10.1 (7.8-12.1)</td>
</tr>
</tbody>
</table>

HR = 0.920 (95%-CI, 0.584 - 1.451) P = 0.72

- No improvement in PFS with mFOLFOXIRI + Panitumumab
- No improvement in PFS across subgroups
- OS data are immature
- G3/4 diarrhoea increased from 12 to 25%
- Increased skin toxicity

Results do not include previous FOLFOXIRI cycles before randomization 
FAS = full analysis set
Secondary resection rates: VOLFI

<table>
<thead>
<tr>
<th></th>
<th>Full Analysis Set</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>96</td>
<td>65</td>
<td>31</td>
</tr>
<tr>
<td>P</td>
<td>0.029</td>
<td>0.088</td>
<td>0.056</td>
</tr>
<tr>
<td>OR</td>
<td>3.63</td>
<td>7.80</td>
<td>5.25</td>
</tr>
<tr>
<td>95%CI</td>
<td>1.13 – 11.67</td>
<td>0.42 – 145.2</td>
<td>1.07 – 25.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Resection Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFOXIRI + P</td>
<td>33.3</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>12.1</td>
</tr>
<tr>
<td>mFOLFOXIRI + P</td>
<td>14.0</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>0</td>
</tr>
<tr>
<td>mFOLFOXIRI + P</td>
<td>75.0</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>36.4</td>
</tr>
</tbody>
</table>
Pan-Asian adapted ESMO algorithm for 1st line treatment of mCRC

**ASSESSMENT OF CLINICAL CONDITION OF THE PATIENT**

- **Fit**
  - GOAL
    - OMD
      - Cytoreduction (Shrinkage)*
        - RAS wt
          - Left sided: CT doublet + anti-EGFR
          - Right sided: CT triplet/doublet + bevacizumab
        - Combination CT + bevacizumab
      - Disease control (Control of progression)
        - RAS wt
          - Left sided: CT doublet + anti-EGFR
          - Right sided: CT doublet + bevacizumab
        - CT doublet + bevacizumab
    - Re-evaluation/assessment of response every 2 months**
      - GOAL
        - Progressive disease
          - Surgery
          - Cytoreduction (Shrinkage)**
            - Continue
        - Disease control
          - Continue; maintenance; or pause
      - Second-line

- **Unfit** (but may be suitable)
  - FP + anti-EGFR; FP + bevacizumab; reduced dose CT doublet; anti-EGFR

- **Unfit**
  - BSC

2017 Pan-Asian adapted ESMO consensus guidelines– Yoshino, Ann Oncol 2018
VOLFI trial

- When Panitumumab is added to FOLFOXIRI it significantly increases tumour response rate (60.0 to 87.3%, p=0.004) but has no impact on PFS or OS possibly because the trial is underpowered.

- The impact on secondary resection from 36.4 to 75% is notable but does not reach statistical significance (p=0.056).

- The response in BRAFm tumours is also interesting (22.2 vs 8.7%, p=0.04) and might be considered as an approach in BRAFm tumours where downsizing for surgery is a clinical objective.

- There are insufficient patient numbers to draw conclusions about the impact of sidedness in the trial.
Pan-Asian adapted ESMO algorithm for 1st line treatment of mCRC

A meta-analysis of triplets versus doublets may provide further valuable insight into these observations from VOLFI and CHARTA.

These studies underline the need for prospective trials to be designed and adequately powered to analyse the impact of treatments on the clinical and molecular subtypes of advanced CRC.