Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A non-inferiority phase III trial: AIO 0207


on behalf of the AIO CRC Study Group
AIO 0207: Background

- The optimal duration of combination chemotherapy with Fluoropyrimidines (FP), oxaliplatin (Ox) and Bevacizumab (Bev) in metastatic colorectal cancer (mCRC) is still unknown.

- Maintenance therapy with FP plus Bev is widely accepted standard – resulting from of chemo-only trials\(^1,2\) and the use in standard arms of clinical trials.\(^3\)

- Recent randomized de-escalation maintenance trials \(^4-7\) have evaluated different regimen, but failed to define a clear standard.

- None of those trials prospectively compared de-escalation doublet vs. single vs. no maintenance.

Objectives

AIO 0207 investigates whether after a 24-week standard induction with any Fluoropyrimidine (FP), oxaliplatin (Ox) and bevacizumab (Bev)

→ no continuation of therapy or
→ continuation with Bev alone
are non-inferior to
→ FP plus Bev
as maintenance treatment
followed by a planned re-induction of (parts of) FP/Ox/Bev as whole treatment strategy
Main endpoints of AIO 0207

Primary endpoint

• Time to failure of strategy (TFS)\(^1\) =
  
  Time from randomization (@ start of maintenance) to either
  
  – 2nd progression after maintenance and re-induction or
  
  – in case of no re-induction after 1st progression: use of a new drug („2nd line“), or no further treatment

Secondary endpoints include

• Progression free survival: Rand → until 1st progression (PFS1)
• Overall survival (OS)
• Toxicity (throughout maintenance treatment); Quality of life
• Biomarker and translational projects


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AIO 0207: Treatment algorithms

Induction: 24 wks

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

Maintenance: non-PD

FP* + Bev
Bev
no treatment

Re-Induction

FP* +/– Oxaliplatin +/– Bev

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

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)

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

Maintenance: non-PD

FP* + Bev
Bev
no treatment

1st progression

No Re-Induction

other drugs(s) / 2nd line
or no further treatment

Stratification
Adjuvant tx.
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PFS1

TFS

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Statistical considerations

- Non-inferiority study - both experimental arms vs. standard arm (FP/Bev)
- 80% power with a one-sided alpha error of 0.0125 for each of the two pairwise comparisons → 148 events per arm needed
- Inferiority margin to be excluded by the confidence interval was set at a median TFS of 3.5 months (assuming a median of 5 months for the standard arm), corresp. to a HR of 1.43
- Time-to-event curves were compared using the logrank test, with all p values being descriptive and two-sided.
Study conduct

AIO sponsored phase III trial
106 sites in Germany
(55 hospital, 51 private practices)

- 852 assessed for eligibility
- 837 eligible
- 829 started induction
- 476 randomized
- 473 randomized and eligible

N=353 (42%) not randomized
- Progression: 124 (35%)
- Mets. Resection: 39 (11%)
- Unacceptable tox.: 53 (15%)
- SAE: 50 (14%)
- Patient's wish: 52 (15%)
- Investigator decision: 30 (8%)
- Death: 28 (8%)

* more than one reason could registered

Accrual: Sept 2009-Feb 2013; Cut-off data 14 Apr 2014 (updated from abstract)

This data set: Median duration of follow-up: 21.3 months; 95% of the randomized patients had completed maintenance treatment

Presented by:
TFS: All arms

Time (months)

Rate without event

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

Log rank test: p=0.099
Non-inferiority testing, vs. FP/Bev

Upper level of non-inferiority: 1.43

No tx., 95% CI

Bev, 95% CI

superior
tolerated level of non-inf.
inferior

HR
0.8 1.0 1.2 1.4 1.6
PFS1 from start of maintenance

Rate without event

Time (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
Re-induction rates and PFS1/TFS

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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
Maintenance trials: combined analysis

**PFS**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Log [Hazard ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard ratio IV, random, 95% CI</th>
<th>Hazard ratio IV, random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>CAIRO3 cape/bev</td>
<td>-0.84397007</td>
<td>0.09065533</td>
<td>27.4%</td>
<td>0.43 [0.36, 0.51]</td>
<td></td>
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<tr>
<td>AIO 0207 FP/bev</td>
<td>-0.71334989</td>
<td>0.12971368</td>
<td>24.1%</td>
<td>0.49 [0.38, 0.63]</td>
<td></td>
</tr>
<tr>
<td>AIO bev</td>
<td>-0.4462871</td>
<td>0.12595133</td>
<td>24.5%</td>
<td>0.64 [0.50, 0.82]</td>
<td></td>
</tr>
<tr>
<td>SAKK4106 bev</td>
<td>-0.28768207</td>
<td>0.13114787</td>
<td>24.0%</td>
<td>0.75 [0.58, 0.97]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.56 [0.43, 0.72]

Heterogeneity: Tau² = 0.05; Chi² = 14.92, df = 3 (P = 0.002); I²=80%
Test for overall effect: Z = 4.42 (P < 0.00001)

**OS**

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</tr>
</thead>
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<tr>
<td>CAIRO3 cape/bev</td>
<td>-0.11653382</td>
<td>0.10111254</td>
<td>47.1%</td>
<td>0.89 [0.73, 1.09]</td>
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<tr>
<td>AIO 0207 FP/bev</td>
<td>-0.01005034</td>
<td>0.16961535</td>
<td>16.8%</td>
<td>0.99 [0.71, 1.38]</td>
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</tr>
<tr>
<td>AIO bev</td>
<td>-0.12783337</td>
<td>0.1705144</td>
<td>16.6%</td>
<td>0.88 [0.63, 1.23]</td>
<td></td>
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<tr>
<td>SAKK4106 bev</td>
<td>-0.18632958</td>
<td>0.15712878</td>
<td>19.5%</td>
<td>0.83 [0.61, 1.13]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.89 [0.78, 1.02]

Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 3 (P = 0.90); I²=0%
Test for overall effect: Z = 1.64 (P = 0.10)
Summary

• Using a TFS strategy, including suggestion for an immediate re-induction, following 6 months with FP/Ox/Bev
  – Maintenance with Bev is non-inferior to FP/Bev
  – Non-inferiority can not be concluded for no active treatment

• Re-induction rates were much lower than expected: 37% overall, decreasing with maintenance intensity

• PFS1 improves with treatment intensity: FP/Bev is better than Bev alone, and this is better than no treatment.

• Preliminary OS showed no difference between treatment arms.

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Conclusions

• In the clinical routine, an *immediate re-induction strategy* – following a 6 mos. induction treatment with FP/Ox/Bev and failure of any de-escalation maintenance - is rarely used even in the defined setting of a clinical trial.

• If time to 1^{st} progression (PFS1) should be prolonged, FP plus Bev is the best treatment option.

• In future, “moderately active” maintenance regimen without symptomatic toxicity may improve outcome and should be further evaluated → next AIO phase III project.
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- AIO study team
AIO 0207 study team

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