Discussion on proffered paper session: Gastrointestinal tumors 1; 1420 & 1430

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Exploratory Oncology Research & Clinical Trial Center,
National Cancer Center, Japan
Disclosure slide

• I have nothing to declare
Papers for discussion


1420: Single-agent capecitabine maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of mCRC

• **Corresponding author:** Ruihua Xu


• **Presented by:** Mingming He

• **Affiliation:** Sun yat-sen university cancer center, China
Maintenance therapy in FOLFOX

**OPTIMOX1**

- **FOLFOX4**
  - L-OHP
  - sLV5FU2

- **FOLFOX7 6cycles**
  - L-OHP
  - sLV5FU2

- **FOLFOX7 reintroduction**
  - L-OHP
  - sLV5FU2

**OPTIMOX2**

- **mFOLFOX7 6cycles**
  - L-OHP
  - sLV5FU2

- **mFOLFOX7 reintroduction**
  - L-OHP
  - sLV5FU2

* duration of disease control

## RCTs evaluating maintenance therapy

<table>
<thead>
<tr>
<th>Trial name</th>
<th>design</th>
<th>Induction chemo (M)</th>
<th>Maintenance</th>
<th>Primary EP HR, p</th>
<th>Primary EP(M)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spanish TTD MACRO</td>
<td>2 arm Non-inferiority N=480</td>
<td>4.5</td>
<td>CapeOX+BEV*</td>
<td>PFS 1.098</td>
<td>10.4</td>
<td>23.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BEV</td>
<td>0.3811</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swiss SAKK</td>
<td>2 arm Non-inferiority N=262</td>
<td>4-6</td>
<td>BEV*</td>
<td>TTP 0.74</td>
<td>4.1</td>
<td>25.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>observation</td>
<td>0.47</td>
<td>2.9</td>
<td>22.8</td>
</tr>
<tr>
<td>Dutch CAIRO3</td>
<td>2 arm superiority N=558</td>
<td>4.5</td>
<td>Cape+BEV</td>
<td>PFS2 0.67</td>
<td>11.7</td>
<td>21.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>observation*</td>
<td>&lt;0.0001</td>
<td>8.5</td>
<td>18.1</td>
</tr>
<tr>
<td>Germany AIO0207</td>
<td>3 arm Non-inferiority N=473</td>
<td>6</td>
<td>FP+BEV*</td>
<td>TFS</td>
<td>6.8</td>
<td>23.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BEV</td>
<td></td>
<td>6.5</td>
<td>26.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>observation</td>
<td></td>
<td>6.1</td>
<td>23.1</td>
</tr>
</tbody>
</table>

*Control arm

Maintenance trials: Combined analysis, vs. no tx.

<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>
</tr>
</thead>
<tbody>
<tr>
<td>AIO 0207</td>
<td>-0.71334889</td>
<td>0.12971368</td>
<td>24.1%</td>
<td>0.49 [0.38, 0.63]</td>
<td></td>
</tr>
<tr>
<td>AIO 0207</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>CAIRO-3</td>
<td>-0.84397007</td>
<td>0.09065533</td>
<td>27.4%</td>
<td>0.43 [0.36, 0.51]</td>
<td></td>
</tr>
<tr>
<td>SAKK</td>
<td>-0.28768207</td>
<td>0.13114787</td>
<td>24.0%</td>
<td>0.75 [0.58, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.56 [0.43, 0.72]</td>
<td></td>
</tr>
</tbody>
</table>

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

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<tbody>
<tr>
<td>AIO 0207</td>
<td>-0.01005034</td>
<td>0.16961535</td>
<td>16.8%</td>
<td>0.99 [0.71, 1.38]</td>
<td></td>
</tr>
<tr>
<td>AIO 0207</td>
<td>-0.12783337</td>
<td>0.1705144</td>
<td>16.6%</td>
<td>0.88 [0.63, 1.23]</td>
<td></td>
</tr>
<tr>
<td>CAIRO-3</td>
<td>-0.11653382</td>
<td>0.10111254</td>
<td>47.1%</td>
<td>0.89 [0.73, 1.09]</td>
<td></td>
</tr>
<tr>
<td>SAKK</td>
<td>-0.18632958</td>
<td>0.15712878</td>
<td>19.5%</td>
<td>0.83 [0.61, 1.13]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.89 [0.78, 1.02]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Study design (#1420)

- Primary endpoint: **Progression-free disease (PFS)**
- Secondary endpoints: **Overall survival (OS), Overall response rate (ORR), Safety.**

Under unavailability of bevacizumab

Xu R and He M, et al: ESMO Asia 2015 (#1420)
This study met primary endpoint

Primary endpoint: PFS (total population)

Secondary endpoint: OS (total population)

Xu R and He M, et al: ESMO Asia 2015 (#1420)
Subgroup analysis: PFS (XELOX / FOLFOX)

**XELOX**

- Maintenance: 10.37 (9.30-13.20) months
- Observation: 7.82 (6.00-9.00) months

**FOLFOX**

- Maintenance: 10.43 (9.60-12.23) months
- Observation: 7.82 (7.03-8.93) months

P-value:

- XELOX: P<0.0001
- FOLFOX: P=0.0013

Xu R and He M, et al: ESMO Asia 2015 (#1420)
# RCTs evaluating maintenance therapy: vs observation

<table>
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<td>FP+BEV*</td>
<td>6.8</td>
<td></td>
<td>23.8**</td>
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<td></td>
<td></td>
<td></td>
<td>BEV</td>
<td>6.5</td>
<td>TFS</td>
<td>26.2**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>observation</td>
<td>6.1</td>
<td></td>
<td>23.1**</td>
</tr>
<tr>
<td>This study</td>
<td>2 arm Superiority N=275</td>
<td>4.5-6</td>
<td>Cape</td>
<td>10.4</td>
<td>PFS2 0.67 &lt;0.0001</td>
<td>23.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>observation*</td>
<td>7.8</td>
<td></td>
<td>19.7</td>
</tr>
</tbody>
</table>

*Control arm  
**OS from the start of maintenance  

Xu R and He M, et al: ESMO Asia 2015 (#1420)
Re-introduction rate of oxaliplatin

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAIRO 3</td>
<td>60%</td>
<td>47% (cape+BV)</td>
</tr>
<tr>
<td>AIO</td>
<td>45%</td>
<td>21% (FL/cape+BV)</td>
</tr>
<tr>
<td>This study</td>
<td>27%</td>
<td>19% (cape)</td>
</tr>
</tbody>
</table>

Xu R and He M, et al: ESMO Asia 2015 (#1420)
Summary & comments (#1420)

- This study firstly showed a significant prolongation of PFS by capecitabine single agent maintenance therapy compared with observation in the 1st line randomized trials.

- Capecitabine monotherapy can be a standard as a maintenance therapy under situation of unavailable for bevacizumab.

- OS benefit is still limited.
High Anus Preservation and Low Toxicity Rates in a Phase I Trial of Neoadjuvant Bowel-Sparing IMRT/Bevacizumab/FOLFOX and TME for Locally Advanced Rectal Cancer

• Jason Chia-Hsien Cheng, Jin-Tung Liang, Chiao-Ling Tsai, Ji-Shiang Hung, John Huang, Yu-Lin Lin, Chia-Chun Wang

• Departments of Oncology and Surgery

• National Taiwan University Hospital

• Taipei, Taiwan
NCCN Guidelines Version 3.2015
Rectal Cancer

CLINICAL STAGE  PRIMARY TREATMENT  ADJUVANT TREATMENT
(6 MO PERIOPERATIVE TREATMENT PREFERRED)

<table>
<thead>
<tr>
<th>T3, N0</th>
<th>Chemo/RT</th>
<th>Transabdominal resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>or T4</td>
<td>Capecitabine/RT or infusional 5-FU/RT or (category 1 and preferred for both)</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>Bolus 5-FU/leucovorin/RT or</td>
<td></td>
</tr>
</tbody>
</table>

Resection contraindicated

FOLFOX (preferred) or CapeOx (preferred) or
FLOX or 5-FU/leucovorin or capecitabine

Active chemotherapy regimen for advanced disease
(See REC-E)

Surveillance
(See REC-B)

Chemotherapy

FOLFOX (preferred) or CapeOx (preferred) or
5-FU/leucovorin or capecitabine

Transabdominal resection

Resection contraindicated

Active chemotherapy regimen for advanced disease
(See REC-E)

Surveillance
(See REC-B)

[Notes: See Principles of Surgery (REC-B). See Principles of Adjuvant Therapy (REC-C). See Principles of Radiation Therapy (REC-D).]


Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.

Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.

FOLFOXIRI is not recommended in this setting.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 3.2015, ©2015 National Comprehensive Cancer Network, Inc., All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.
Methods

• Eligibility
  • Age < 70 MRI and PET staged T3-4 or N+M0 rectal adenocarcinoma within 12 cm from anal verge

• Treatment
  • **Bevacizumab 5 mg/kg on day 1, 15, 29**
  • **Oxaliplatin 40 mg/m²; leucovorin 400; 5-fluorouracil (5-FU) bolus 400 mg /m² followed by 2400 mg/m² IV continuous infusion over 46 hours at week 1, 3, 5**
  • **IMRT** : 1.8 → 2.0 → 2.2 Gy per fraction for 25 fractions
    • Rectal tumor dose level 1: 45 Gy (5 patients) → level 2: 50 Gy (5 patients) → level 3: 55 Gy (5 patients) (45 Gy to pelvic lymphatics)
  • **Surgery (TME)** at 6-10 weeks after completion of CCRT

CAO/ARO/AIO-04 trial

Best arm of CAO/ARO/AIO-94

RT 50.4 Gy + 5-FU (n=623)
1000 mg/m² days 1-5 + 29-33

5-FU
500 mg/m² d 1-5, q29
4 cycles (4 months)

Based on phase I/II trials:

RT 50.4 Gy + 5-FU/OX (n=613)
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinic Acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)

Note: Chemo gap 3rd week of RT!
3-year DFS: 71.2% vs. 75.9%
HR: 0.79   P=0.03

3-year OS: 88.7% vs. 88.0%
HR: 0.96

Rectal adenocarcinoma cT3/4 and/or cN+, cM0 PS 0-2

PETACC-6

Cape+RT → TME → Adj Cape

Cape+LOHP+RT → TME → Adj Cape+LOHP (CapeOX)

Disease-free survival: PETACC-6

Cox model adjusted for stratification factors (except center)
HR = 1.04; 95% CI: (0.81,1.33)
P-value = 0.781
3-year DFS: 74.5% in Cape+RT vs. 73.9% in Cape+Oxali+RT

OADORE trial

FP+RT → TME → ypStageII → ypStageIII → R → Adjuvant 5-FU/LV → Adjuvant FOLFOX

Disease-free survival: ADORE

Controversies in pre-ope CRT for rectal cancer

- Adding oxaliplatin in pre-ope CRT is controversial

- Post-ope FOLFOX might yield survival advantage compared with fluoropyrimididine alone

- No confirmatory evidences of bevacizumab radio-sensitizing effect

- No. of clinical trials with IMRT is still limited
Results (Survival Outcomes)

- **pCR rate:** 5/15 (33%) (3 with 55Gy; 2 with 45Gy)
- 14/15 (93%) with T or N downstaging effect
  - 11/15 (73%) with T and 12/15 (80%) with N downstaging
- **14 / 15 patients with anal preservation (13 functional)**
- 1 anal incontinence in the 45 Gy group
- 1 gangrene of scrotum (tumor invasion to seminal vesicle) in the 55 Gy group, s/p debridement
- No death or local recurrence yet, one liver metastasis s/p RFA with disease free again in the 50-Gy group
- 3-year disease free survival : 83%
## Addition of oxaliplatin in pre-ope CRT: pCR rate

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts</th>
<th>ChemoRT Regimen</th>
<th>yCR Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD 12 (JCO 2010)</td>
<td>291</td>
<td>Cape +RT</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>293</td>
<td>Cape +Oxali (50mg/m² wkly) +RT</td>
<td>19 (p=0.09)</td>
</tr>
<tr>
<td>STAR-01 (JCO 2011)</td>
<td>379</td>
<td>5FU CI +RT</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>368</td>
<td>5FU CI +Oxali (60mg/m² wkly) +RT</td>
<td>16 (p=NS)</td>
</tr>
<tr>
<td></td>
<td>613</td>
<td>5FU CI +Oxali (50mg/m² wkly) +RT</td>
<td>17 (p=0.04)</td>
</tr>
<tr>
<td>PETACC-06 (ASCO 2013)</td>
<td>547</td>
<td>Cape +RT</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>547</td>
<td>Cape +Oxali (50mg/m² wkly) +RT</td>
<td>14 (p=0.27)</td>
</tr>
<tr>
<td>NSABP R-04 (JCO 2014)</td>
<td>636</td>
<td>5FU/Cape +RT</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>640</td>
<td>5FU/Cape +Oxali (50mg/m² wkly) +RT</td>
<td>20 (p=0.42)</td>
</tr>
</tbody>
</table>
Issues raised in the study (#1430)

- Adding oxaliplatin in pre-ope CRT is necessary?
- How to evaluate the benefit of IMRT and radio-sensitizing effect of Bev?
- What is the next study design?

Waiting for the next step of the big challenge