ESMO PRECEPTORSHIP ON COLORECTAL CANCER

20-21 OCTOBER 2017
BARCELONA, SPAIN
Locoregional therapy for liver metastases

Michel Ducreux
ESMO consensus on mCRC 2016

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A Cervantes

Co-Chairs of working groups  
A Sobrero  
R Adam  
H Van Krieken

Advanced mCRC  
Local and ablative treatment, oligometastasis  
Molecular Pathology and Biomarkers

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R Salazar  
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H Wassan  
T Yoshino  
A Zaanan
HAI: rational

- Colorectal cancer (CRC): liver is usually the 1st site of mets
  - Hematogenic spread: portal vein → liver → lung → other organs (1541 CRC necropsies ¹)
  - Eradicate colorectal liver metastases (CRLM) by locoregional treatments (surgery, RFA, HAI,…) may limit extrahepatic metastatic spreading

- Vascularization
  - Animal models¹
    - CRLM: almost exclusively by hepatic artery (e.p. if > 3 cm)
    - Normal liver: preferentially by portal vein

HAI: rationale
# HAI: rational

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life</th>
<th>Increase exposure by HAI (fold increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floxuridin (FUDR)</td>
<td>&lt; 10 mn</td>
<td>100-400</td>
</tr>
<tr>
<td>5-fluoro-uracil (5FU)</td>
<td>10 mn</td>
<td>5-10</td>
</tr>
<tr>
<td>Bischloro-éthyl-nitroso-urea</td>
<td>&lt; 5 mn</td>
<td>6-7</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>≤ 10 mn</td>
<td>6-8</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>15-19 h</td>
<td>4-5</td>
</tr>
</tbody>
</table>

HAI: A way to intensify chemotherapy...
HAI: procedures

1. Surgery
   • Catheter inserted during surgical procedures
   • Mostly into the gastroduodenal artery (GDA)
   • Connected to port system placed onto right costal

2. Mini-invasive: interventional radiology
   • Transfemoral
   • Angiography
   • Catheter inserted into the GDA
   • GDA obstructed by coils, KT blocked
   • Lateral holes of the KT placed into the common hepatic artery
   • Branches to duodenum and lower 1/3 of stomach are embolized
Old fashion
Recent methods
HAI: complications

Systematic review (1950-2001, 101 studies, 4580 patients)

- Mortality: 1%

- Morbidity
  - Gastrointestinal: 22% (e.p. 5FU)
  - Hepatitis: 19%, biliary toxicity (e.p. FUDR)
  - Hematotoxicity: 8% (e.p. 5FU)
  - HA Obstruction: 6%
  - HAI catheter thrombosis: 5%
  - HAI catheter migration: 7%

Barnett KT, Malafa MP. Int J Gastrointest Cancer 2001;30:147-60
Palliative HAI

Fluoropyrimidine-HAI (hepatic arterial infusion) versus systemic chemotherapy (SCT) for unresectable liver metastases from colorectal cancer (Review)

Mocellin S, Pasquali S, Nitti D
Palliative HAI

Méta-analysis, Cochrane 2009 (10 trials)

Forest plot of risk ratio for tumor response (all trials).
HAI : hepatic arterial infusion – SCT : systemic chemotherapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HAI</th>
<th>SCT</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Kemeny 1987</td>
<td>24</td>
<td>45</td>
<td>10</td>
<td>48</td>
</tr>
<tr>
<td>Martin 1990</td>
<td>15</td>
<td>31</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Wagman 1990</td>
<td>17</td>
<td>31</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Lorenz 2000</td>
<td>34</td>
<td>77</td>
<td>14</td>
<td>52</td>
</tr>
<tr>
<td>Kerr 2003</td>
<td>17</td>
<td>77</td>
<td>20</td>
<td>108</td>
</tr>
<tr>
<td>Kemeny 2006</td>
<td>28</td>
<td>59</td>
<td>14</td>
<td>58</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>461</td>
<td>440</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>198</td>
<td>81</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hererogeneity: Chi² = 12.20, df = 8 (P = 0.14); l² = 34%
Test for overall effect: Z = 7.03 (P < 0.00001)
Palliative HAI

Méta-analysis, Cochrane 2009 (10 trials)

Forest plot of hazard ratio for overall survival (all trials).
HAI: hepatic arterial infusion – SCT: systemic chemotherapy

<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>Year</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemeny 1987</td>
<td>-0.386</td>
<td>0.198</td>
<td>7.6%</td>
<td>0.68 [0.46, 1.00]</td>
<td>1987</td>
<td></td>
</tr>
<tr>
<td>Chang 1987</td>
<td>0.11</td>
<td>0.077</td>
<td>11.5%</td>
<td>1.12 [0.96, 1.30]</td>
<td>1987</td>
<td></td>
</tr>
<tr>
<td>Hohn 1989</td>
<td>0.107</td>
<td>0.0811</td>
<td>11.3%</td>
<td>1.11 [0.95, 1.30]</td>
<td>1989</td>
<td></td>
</tr>
<tr>
<td>Wagman 1990</td>
<td>0.1179</td>
<td>0.1002</td>
<td>10.8%</td>
<td>1.13 [0.92, 1.37]</td>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>Martin 1990</td>
<td>0.1211</td>
<td>0.1204</td>
<td>10.1%</td>
<td>1.13 [0.89, 1.43]</td>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>Rougier 1992</td>
<td>-0.406</td>
<td>0.152</td>
<td>9.1%</td>
<td>0.67 [0.49, 0.90]</td>
<td>1992</td>
<td></td>
</tr>
<tr>
<td>Allen 1994</td>
<td>-0.528</td>
<td>0.092</td>
<td>11.0%</td>
<td>0.59 [0.49, 0.71]</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>Lorenz 2000</td>
<td>-0.0397</td>
<td>0.217</td>
<td>7.1%</td>
<td>0.96 [0.63, 1.47]</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>Kerr 2003</td>
<td>0.112</td>
<td>0.0616</td>
<td>11.8%</td>
<td>1.12 [0.99, 1.26]</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Kemeny 2006</td>
<td>-0.386</td>
<td>0.135</td>
<td>9.7%</td>
<td>0.68 [0.52, 0.89]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100%</td>
<td>0.90 [0.76, 1.07]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hererogeneity: \( \text{Tau}^2 = 0.06, \text{Chi}^2 = 60.83, \text{df} = 9 \ (P < 0.00001); \ I^2 = 85\%

Test for overall effect: \( Z = 1.17 \ (P = 0.24) \)

Palliative HAI
Phase II trial

- 1999-2001
- 6 centres
- Inclusion criteria
  - Non-resectable CRLM
  - No extrahepatic disease
  - Oxaliplatin-naïve

HAI oxaliplatin + iv LV5FU2

ORR: 64%

5 surgical resections
Extrahepatic PD: 8 pts

Follow-up: 23 months
PFS: 27 months
OS: 27 months

=> HAI Oxaliplatin: feasible and effective

Palliative HAI
HAI oxaliplatin + iv LV5FU2-cetuximab 1\textsuperscript{st} line

- Phase II CHOICE (8 centres)
- 35 patients, 1\textsuperscript{st} line
  - Non-resectable CRLM
  - \textit{KRAS} \textsuperscript{WT}: 30/35 (86%)
- ORR: 88\% (CR: 3\%)
  - \textit{KRAS}/BRAF \textsuperscript{WT}: 96\%
- DCR: 97\%
  - \textit{KRAS}/BRAF \textsuperscript{WT}: 100\%
- Resection: 66\% (23/35)
  - \textit{KRAS}/BRAF \textsuperscript{WT}: 74\%

Nice exemple CHOICE

Before

After

Refractory mCRC

- 2000-2004
- N=44
- Nb cycles = 9 [0-25]

⇒ HAI Oxaliplatin: feasible and effective after systemic chemotherapy failure, even after systemic oxaliplatin

Same experience with 3 drugs... and more hevalily pretreated patients

Oxaliplatin + 5FU + irinotecan IAH + cetuximab IV ≥2nd line

Multicentric international phase II « OPTILIV »
- 64 patients with non resectable LMCRC, KRAS WT
- Median: 10 LM involving 6 segments
- 41%: 1-3 extra-liver metastases < 1 cm

<table>
<thead>
<tr>
<th>Prior chemotherapy drugs</th>
<th>n of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>61 (95%)</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>50 (78%)</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>40 (63%)</td>
</tr>
<tr>
<td>Both Irinotecan and Oxaliplatin</td>
<td>26 (41%)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>21 (33%)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>40 (63%)</td>
</tr>
<tr>
<td>Both Cetuximab and Bevacizumab</td>
<td>12 (19%)</td>
</tr>
</tbody>
</table>

In these patients also ETS is better...

Oxaliplatin + 5FU + irinotecan IAH + cetuximab IV ≥2nd line

Secondary resection in a mixed population

- N= 87
- Non resectable CRLM
- HAI Oxaliplatin + IV 5-FU
- Chemotherapy-naive: 18 (21%)
- N cycles: 8 [0-25]

23 patients (26%): CRLM resection
21 curative resections

HAI: initial treatment in 43% of operated pts vs. 14% of non-operated pts (p=.004)

Secondary resection in a mixed population

3y-OS: 73%
5y-OS: 56%

Median follow-up: 63 months

Operated pts: median OS, 42 months

HAI oxaliplatin with iv 5-FU offers a second chance to remove initially unresectable CRLM in 24% of patients, even after failure of prior ‘modern’ systemic CTx. Long-term OS can be obtained with this approach.

Even in more advanced disease...

Oxaliplatin + 5FU + irinotecan IAH + cetuximab IV ≥2<sup>nd</sup> line

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Prior chemotherapy protocols</th>
<th></th>
<th></th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=64)</td>
<td>1 line (n=28)</td>
<td>2-3 lines (n=36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (2%)</td>
<td>1 (4%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>25 (39%)</td>
<td>9 (32%)</td>
<td>16 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>28 (44%)</td>
<td>12 (43%)</td>
<td>16 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>3 (5%)</td>
<td>1 (4%)</td>
<td>2 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>7 (11%)</td>
<td>5 (18%)</td>
<td>2 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>41%</td>
<td>36%</td>
<td>44%</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>DCR</td>
<td>84%</td>
<td>79%</td>
<td>89%</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>R0-R1 resection</td>
<td>30%</td>
<td>46%</td>
<td>17%</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>PFS (mo) [95% CI]</td>
<td>9.3 [7.8-10.9]</td>
<td>10.1 [7.8-12.3]</td>
<td>8.5 [5.8-11.2]</td>
<td>0.088</td>
<td></td>
</tr>
<tr>
<td>OS (mo) [95% CI]</td>
<td>25.5 [18.8-32.1]</td>
<td>31.8 [26.0-37.6]</td>
<td>15.7 [10.1-21.2]</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Conversion to Resectability Using Hepatic Artery Infusion Plus Systemic Chemotherapy for the Treatment of Unresectable Liver Metastases From Colorectal Carcinoma


HAI conclusion

- FUDR, 5FU: modest OS benefit (if any)
- Oxaliplatin: feasibility & tolerance > FUDR
- ‘Intensified’ HAI-IV combos: ORR > 80%, DCR ~100%
- Even after systemic chemotherapy failure
- Conversion to resectability: up to 74% of pts with CRLM
- But it remains quite experimental
Adjuvant HAI

- After resection of CRLM
- Liver Recurrence: 30-50%

- Adjuvant CTx with systemic 5 FU

- Perioperative CTx with FOLFOX for pts with ≤ 3 CRLM (EORTC)

3y-DFS: 28% vs 36%, p=0.04

Portier et al, J Clin Oncol 2006
Mitry et al, J Clin Oncol 2008
Nordlinger et al, Lancet 2008
Adjuvant HAI

Méta-analysis, Cochrane 2009 (n = 7)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hepatic Artery Chemo N</th>
<th>Control N</th>
<th>Log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemeny 1999</td>
<td>74</td>
<td>82</td>
<td>-0.051 (0.2205)</td>
<td></td>
<td>22.2%</td>
<td>0.95 [0.62, 1.46]</td>
</tr>
<tr>
<td>Kemeny 2002</td>
<td>53</td>
<td>56</td>
<td>0.3382 (0.2182)</td>
<td></td>
<td>22.7%</td>
<td>1.40 [0.91, 2.15]</td>
</tr>
<tr>
<td>Lorenz 1998</td>
<td>113</td>
<td>113</td>
<td>0.1988 (0.167)</td>
<td></td>
<td>38.7%</td>
<td>1.22 [0.88, 1.69]</td>
</tr>
<tr>
<td>Lygidakis 1995</td>
<td>20</td>
<td>20</td>
<td>-0.8059 (0.3766)</td>
<td></td>
<td>7.6%</td>
<td>0.45 [0.21, 0.93]</td>
</tr>
<tr>
<td>Rudroff 1999</td>
<td>14</td>
<td>16</td>
<td>0.2885 (0.4017)</td>
<td></td>
<td>6.7%</td>
<td>1.33 [0.61, 2.93]</td>
</tr>
<tr>
<td>Tono 2000</td>
<td>9</td>
<td>10</td>
<td>-0.8004 (1.0169)</td>
<td></td>
<td>1.0%</td>
<td>0.45 [0.06, 3.30]</td>
</tr>
<tr>
<td>Wagram 1990</td>
<td>6</td>
<td>5</td>
<td>-0.6293 (1.0483)</td>
<td></td>
<td>1.0%</td>
<td>0.53 [0.07, 4.16]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.09 [0.89, 1.34]</td>
</tr>
</tbody>
</table>

Hererogeneity: Chi² = 9.27, df = 6 (P = 0.16); I² = 35%
Test for overall effect: Z = 0.83 (P = 0.41)

Nelson RL, Freels S. Cochrane Database System Rev 2009
Adjuvant HAI

HAI oxaliplatin

- IGR prospective database (2000-09)

- 98 patients
  - OR/SD after preop CTx
  - ≥ 4 resected CRLM
  - ≥ 1 adjuvant CTx cycle

- Treatment
  - HAI oxaliplatin, n = 44
  - IV FOLFOX or FOLFIRI, n = 54

- Median follow-up: 45 months

---

<table>
<thead>
<tr>
<th></th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>HAI vs IV</td>
<td>0.37 [0.23-0.60]</td>
</tr>
<tr>
<td>R0 resection</td>
<td>0.47 [0.29-0.76]</td>
</tr>
</tbody>
</table>

Logrank: chi2 à 1 ddl = 15.781, p < 0.0001

Adjuvant HAI: PACHA-01

Postoperative hepatic Arterial Chemotherapy in High-risk patients as Adjuvant treatment after resection of colorectal liver metastases

Sponsor: Gustave Roussy - PI: D Goéré - Co-PI: D Malka

Multicenter, randomised Phase 2-3 trial (PHRC 2013)

Isolated CRLM (except ≤ 3 resectable lung nodules)
≥ 4 operated CRLM
- Resection/ablation
- R0 (« potentially » if RFA)

Preoperative CTx
- Oxaliplatin and/or irinotecan
- ± anti-EGFR/antiangiogenic
- ORR or SD

OMS 0-1
≥ 18 yrs

Stratification
- Preop oxaliplatin (O/N)
- Preop CTx duration (≤ 3 vs > 3 m)
- Response to preop CTx (OR vs SD)
- Nb of treated CRLM (4-8 vs >8)
- Centre

Endpoints
- Primary: 18-month hepatic RFS (30% → 50%)
  - Phase 3
    - 3-yr RFS (15% → 30%; HR: 0.63)
    - 220 patients (+106)
- Secondary: feasibility (≥ 4 cycles), tolerance, RFS, OS

iv mFOLFOX6

Start ≤ 8 weeks postoperatively
Duration: ≥ 3 m; maximum: 6 m
Targeted therapy: allowed if received preop

HAI oxaliplatin + iv LV5FU2

n = 114

R
Use of IAHC??

Diagnosis of LMCRC

Resectables immediately or secondary

Neoadjuvant Chemotherapy

Surgery

Resectable limit/Potentially Resectables

Non resectables

OSCAR

First line

Second line

SULTAN

IAHC

IAH

PACHA

Adjuvant Therapy

4th line
Intraarterial Therapy with Yttrium 90: TheraSphere®
Concept of Selective Internal Radiation Therapy (SIRT)

- To **selectively target** a very high radiation dose to all tumours within the liver, regardless of their cell of origin or location, while at the same time maintaining a low radiation dose to the normal liver tissue.

- Infusion via hepatic artery, using differential blood supply to liver tumours thereby preferentially targeting tumours.

- Uses $^{90}$Yttrium-labelled SIR-Spheres® microspheres:
  - Diameter approx. 30 µm (microns)
  - Half life: 64 hours
  - Beta 0.93 MeV
  - Penetrates mean 2.5 mm tissue; max 11 mm
  - Doses of 100–1,000+ Gy to the tumour.
Overview of SIRT Procedure

- Typically a 2-stage process
- Work-up procedure:
  - Trans-femoral catheter access to hepatic artery vasculature and identify tumour feeding vessels
  - Prophylactic occlusion of extra-hepatic vessels (GDA, right gastric etc)
  - Injection of $^{99m}$Tc-MAA / gamma camera study to assess lung shunt
- Treatment procedure:
  - 1–3 weeks later
  - Reassessment of occlusion
  - Injection of SIR-Spheres microspheres
  - Optional gamma camera study to confirm implantation
  - Sequential lobar approach if necessary
Radioembolisation

Eligible Patients
Liver-limited mCRC refractory to chemotherapy

Stratification
Institution
Interval to progression on chemotherapy

Random Assignment
Arm A
5FU protracted IV infusion (300 mg/m² D1-14 q3w)
Until progression
Y resin microspheres

Arm B
Y resin microspheres D1 cycle 1 + 5FU protracted IV infusion (225 mg/m² D1-14, cycle 1; 300 mg/m² D1-14 q3w thereafter)
Until progression

Best Overall Hepatic Response

<table>
<thead>
<tr>
<th>Response</th>
<th>FU Alone (n=23)</th>
<th>Radioembolization + FU (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Nonevaluable</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

NOTE. Comparison of response rates: 0 of 23 versus two of 21, P=.22 (95% CI for the difference between arms B and A ranging from -0.10 to 0.32). Comparison of stabilization rates: eight of 23 versus 18 of 21, P=.001 (95% CI for the difference ranging from 0.19 to 0.71).

Time to Liver Progression, Time to Progression Overall, and Overall Survival

<table>
<thead>
<tr>
<th>Time to Progression and OS</th>
<th>FU Alone (n=23)</th>
<th>Radioembolization + FU (n=21)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTLP, median, months</td>
<td>2.1</td>
<td>5.5</td>
<td>0.38</td>
<td>0.20 to 0.72</td>
<td>.003</td>
</tr>
<tr>
<td>Patients with treatment change censored at the time of change</td>
<td>2.1</td>
<td>5.6</td>
<td>0.35</td>
<td>0.18 to 0.69</td>
<td>.002</td>
</tr>
<tr>
<td>TTP, median, months</td>
<td>2.1</td>
<td>4.5</td>
<td>0.51</td>
<td>0.28 to 0.94</td>
<td>.03</td>
</tr>
<tr>
<td>OS, median, months</td>
<td>7.3</td>
<td>10.0</td>
<td>0.92</td>
<td>0.47 to 1.78</td>
<td>.80</td>
</tr>
</tbody>
</table>

SIR-Spheres microspheres + FOLFOX4 in mCRC: CT Response

Patient 2: Baseline CT scan pre-SIRT

Patient 2: CT scan 6 months post-SIRT

Sharma et al. WCGIC Ann Oncol 2006;17(Sup 6):vi78 Abs P-191. Data on file; Sirtex Medical Limited.
SIRFLOX : mCRC L1

- Randomized phase II trial
  - Stratification factors: LLD vs non LLD, <25% or > 25% of liver involvement

- Accrual 2007-2013
- Median follow-up 36 months
- **Main endpoint** : PFS
- **Secondary endpoints** :
  - RR, liver PFS, secondary resection, toxicity...

SIRFLOX : Results

### PFS

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX (+bev)</td>
<td>263</td>
<td>225</td>
<td>10.2</td>
</tr>
<tr>
<td>FOLFOX (+bev) + SIRT</td>
<td>267</td>
<td>217</td>
<td>10.7</td>
</tr>
</tbody>
</table>

**HR:0.93** (95% CI:0.77-1.12)  
**p=0.43**

### Liver PFS

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX (+bev)</td>
<td>263</td>
<td>12.6</td>
</tr>
<tr>
<td>FOLFOX (+bev) + SIRT</td>
<td>267</td>
<td>20.5</td>
</tr>
</tbody>
</table>

**HR:069** (95% CI:0.55-0.90)  
**p=0.002**

- 7.9 month improvement in median PFS in the liver
- 31% reduction in risk of disease progression in the liver

## SIRFLOX : Results

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>Liver PFS</th>
<th>RR</th>
<th>Liver RR (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>10.2</td>
<td>12.6</td>
<td>68%</td>
<td>69% (2%)</td>
</tr>
<tr>
<td>CT + SIRT</td>
<td>10.7</td>
<td>20.5</td>
<td>76%</td>
<td>79% (6%)*</td>
</tr>
<tr>
<td>HR, p</td>
<td>0.93, NS</td>
<td>0.69, p=.002</td>
<td>p=.11</td>
<td>p=.04 (.02)</td>
</tr>
</tbody>
</table>

*Similar rate of liver resection between the two groups (14%)  
Grade >2 toxicity increased in group SIRT: +10% haematologic and GI toxicities

## Conclusion :

- Negative study on its main endpoint  
- Positive in terms of liver disease control  
- + 8 months in liver PFS  
- Wait for OS results and pooled analysis of all the trials with this compound SIRFLOX, FOXFIRE  

First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials

Harpreet SWason*, Peter Gibbs*, Navesh K Sharma, Julien Taieb, Volker Heinemann, Jens Ricke, Marc Peeters, Michael Findlay, Andrew Weaver, Jamie Mills, Charles Wilson, Richard Adams, Anne Francis, Joanna Moschandreou, Pradeep S Virdee, Peter Dutton, Sharon Love, Val Gebski, Alastair Gray, FOXFIRE trial investigator†, SIRFLOX trial investigator†, FOXFIRE-Global trial investigator†, Guy van Hazel*, Ricky A Sharma*

The study design

The FOXFIRE, SIRFLOX and FOXFIRE Global studies share a similar design

Prospective open-label multi-center international RCTs

Eligible Patients
- Non-resectable liver-only or liver-dominant mCRC
- No prior chemo for advanced disease
- Fit for combination therapy and selective internal radiation therapy (SIRT)

Stratified by
- Presence of extra-hepatic metastases
- Degree of liver involvement
- Intended use of biologic agent
- Institution

Randomised
1:1
n = 1,103

mFOLFOX6/OxMdG ± biologic
n = 554

SIR-Spheres
Y90 resin microspheres

mFOLFOX6/OxMdG ± biologic
n = 549

Biologic agents:
- Bevacizumab in SIRFLOX and FOXFIRE Global
- Bevacizumab or cetuximab in the FOXFIRE study.

Biologics allowed at investigator’s discretion, per institutional practice.

The study schemas:

<table>
<thead>
<tr>
<th>SIRFLOX</th>
<th>FOXFIRE Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment protocol</td>
<td></td>
</tr>
<tr>
<td>• SIRT at cycle 1 (or 2)</td>
<td>• SIRT at cycle 2</td>
</tr>
<tr>
<td>• Bevacizumab allowed from c1 in control and c4 in experimental arm</td>
<td>• Bevacizumab / cetuximab allowed from c1 in control and c7 in experimental arm</td>
</tr>
<tr>
<td>• Treatment till Progression</td>
<td>• Treatment for up to 12 cycles (6M)</td>
</tr>
</tbody>
</table>

Virdee PS et al. JMW Res Protoc 2017; 6:e43.
FOXFIRE OS combined analysis

Overall Survival (n= 1,103)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>549</td>
<td>411</td>
<td>23.3 months</td>
</tr>
<tr>
<td>Chemo + SIRT</td>
<td>554</td>
<td>433</td>
<td>22.6 months</td>
</tr>
</tbody>
</table>

HR: 1.04 (95% CI: 0.90–1.19)
p= 0.609

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Chemo</th>
<th>Chemo + SIRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>549</td>
<td>554</td>
</tr>
<tr>
<td></td>
<td>419</td>
<td>417</td>
</tr>
<tr>
<td></td>
<td>242</td>
<td>247</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>17</td>
</tr>
</tbody>
</table>

*Biologic agents: Bevacizumab in SIRFLOX and FOXFIRE Global. Bevacizumab or cetuximab in the FOXFIRE study. Biologicals allowed at investigator’s discretion, per institutional practice.

Isolated CRLM, failure of 2 (64%) or 3 (36%) lines of systemic CTx \( (n = 74) \)

- Primary objective: increase 2-yr OS by 40% (HR: 0.72)

**Italian Phase III**

TACE: DEBIRI \( (x \ 2 \ at \ 1\)-month interval) \( (n = 36) \)

DEBIRI: Drug-Eluting Beads + irinotecan (200 mg)

FOLFIRI \( (x \ 8) \)
\( (n = 38) \)

TACE

### OS

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>ORR</th>
<th>PFS</th>
<th>Toxicity Early (G2/3)</th>
<th>Late (G2)</th>
<th>Increase in QOL*</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEBIRI</td>
<td>22 m</td>
<td>69%</td>
<td>7 m</td>
<td>70%**</td>
<td>20%</td>
<td>60%</td>
<td>5000 € (2 Deb)</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>15 m</td>
<td>20%</td>
<td>4 m</td>
<td>25%</td>
<td>80%</td>
<td>22%</td>
<td>18000 € (8 CTx)</td>
</tr>
</tbody>
</table>

* Median follow-up: 50 months (range: 26-64)
** Edmonton score compared to baseline
** pain, vomiting, fatigue

Conclusion: a lot of non-evidence based medicine!!

- HAI catheters and HAI CTx
  - HAI KT: easy for surgeons, learning curve for interventional radiologists
  - HAI CTx: more demanding than systemic CTx

- HAI oxaliplatin
  - Better tolerated, more convenient and at least as effective than FUDR
  - A peculiar and frequent AE: pain during infusion
  - Adjuvant setting: RFS, to be confirmed by a randomized trial
  - Palliative setting:
    - Highly effective in oxaliplatin-naïve pts (FNLCC, CHOICE)
    - Effective in 2nd line and beyond, even after failure of oxaliplatin-based systemic CTx

- RE, TACE
  - Effective in 2nd line and further
  - 1st line?
  - + systemic CTx?

SBRT:
- Different problem
- Local physical treatment
- A new tool (vs RFA, microwave or surgery)