ESMO PRECEPTORSHIP ON COLORECTAL CANCER

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

Michel Ducreux
Disclosure

- Participation to advisory boards:
  - ROCHE
  - MERCK SERONO
  - AMGEN
  - SANOFI
  - BAYER
  - LILLY
  - CELGENE
  - SERVIER

- Speaker in symposiums:
  - ROCHE
  - MERCK SERONO
  - SANOFI
  - LILLY
  - CELGENE

- Research funding:
  - ROCHE
  - MERCK SERONO
  - PFIZER
ESMO consensus on mCRC 2016

**Chairs:**
- E Van Cutsem
- D Arnold
- A Cervantes

**Co-Chairs of working groups**
- A Sobrero: Advanced mCRC
- R Adam: Local and ablative treatment, oligometastasis
- H Van Krieken: Molecular Pathology and Biomarkers

**Contributors**

<table>
<thead>
<tr>
<th>Aderka</th>
<th>Heinemann</th>
<th>Price</th>
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<tbody>
<tr>
<td>Aranda</td>
<td>Hoff</td>
<td>Punt</td>
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<tr>
<td>Bardelli</td>
<td>Köhne</td>
<td>Ricke</td>
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<td>Benson</td>
<td>Labianca</td>
<td>Roth</td>
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<td>Bodoky</td>
<td>Laurent-Puig</td>
<td>Salazar</td>
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<td>Ciardiello</td>
<td>Ma</td>
<td>Scheithauer</td>
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<td>D’Hoore</td>
<td>Maughan</td>
<td>Schmoll</td>
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<td>Diaz Rubio</td>
<td>Muro</td>
<td>Tabernero</td>
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<td>Douillard</td>
<td>Normanno</td>
<td>Taieb</td>
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<td>Ducreux</td>
<td>Österlund</td>
<td>Tejpar</td>
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<td>Falcone</td>
<td>Oyen</td>
<td>Wassan</td>
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<td>Grothey</td>
<td>Papamichael</td>
<td>Yoshino</td>
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<td>Gruenberger</td>
<td>Pentheroudakis</td>
<td>Zaanan</td>
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<td>Haustermans</td>
<td>Pfeiffer</td>
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</table>
HAI: rational

- Colorectal cancer (CRC): liver is usually the 1\textsuperscript{st} site of mets
  - Hematogenic spread: portal vein $\rightarrow$ liver $\rightarrow$ lung $\rightarrow$ other organs (1541 CRC necropsies \(^1\))

  $\rightarrow$ Eradicate colorectal liver metastases (CRLM) by locoregional treatments (surgery, RFA, HAI,...) may limit extrahepatic metastatic spreading

- Vascularization
  Animal models\(^1\)
  - CRLM: almost exclusively by hepatic artery (e.p. if > 3 cm)
  - Normal liver: preferentially by portal vein

HAI: rationale

Breedis C et al.
Am J Pathol. 1954
Sep-Oct;30(5):969-77
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 arc

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
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 Events</th>
<th>HAI Total</th>
<th>SCT Events</th>
<th>SCT Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemeny 1987</td>
<td>24</td>
<td>45</td>
<td>10</td>
<td>48</td>
<td>12.0%</td>
<td>2.56 [1.38, 4.74]</td>
<td>1987</td>
<td></td>
</tr>
<tr>
<td>Martin 1990</td>
<td>15</td>
<td>31</td>
<td>6</td>
<td>29</td>
<td>7.7%</td>
<td>2.34 [1.05, 5.20]</td>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>Wagman 1990</td>
<td>17</td>
<td>31</td>
<td>2</td>
<td>10</td>
<td>3.7%</td>
<td>2.74 [0.76, 9.86]</td>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>Lorenz 2000</td>
<td>34</td>
<td>77</td>
<td>14</td>
<td>52</td>
<td>20.7%</td>
<td>1.64 [0.98, 2.74]</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>Kerr 2003</td>
<td>17</td>
<td>77</td>
<td>20</td>
<td>108</td>
<td>20.6%</td>
<td>1.19 [0.67, 2.12]</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Kemeny 2006</td>
<td>28</td>
<td>59</td>
<td>14</td>
<td>58</td>
<td>17.5%</td>
<td>1.97 [1.16, 3.34]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>461</td>
<td>440</td>
<td>100%</td>
<td></td>
<td></td>
<td>2.26 [1.80, 2.84]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>198</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Herogeneity: \( \chi^2 = 12.20, \text{df} = 8 (P = 0.14); I^2 = 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</th>
<th>Year</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random, 95% CI</td>
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<td></td>
</tr>
<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>
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<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>
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</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: Tau² = 0.06, Chi² = 60.83, df = 9 (P < 0.00001); I² = 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 1st line

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

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\textsuperscript{nd} line

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Prior chemotherapy protocols</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All (n=64)</td>
<td>1 line (n=28)</td>
<td>2-3 lines (n=36)</td>
<td>p</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>
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<tr>
<td>SD</td>
<td>28 (44%)</td>
<td>12 (43%)</td>
<td>16 (44%)</td>
<td></td>
<td></td>
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<tr>
<td>PD</td>
<td>3 (5%)</td>
<td>1 (4%)</td>
<td>2 (6%)</td>
<td></td>
<td></td>
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<tr>
<td>NE</td>
<td>7 (11%)</td>
<td>5 (18%)</td>
<td>2 (6%)</td>
<td></td>
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</tr>
<tr>
<td>ORR</td>
<td>41%</td>
<td>36%</td>
<td>44%</td>
<td>ns</td>
<td></td>
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<tr>
<td>DCR</td>
<td>84%</td>
<td>79%</td>
<td>89%</td>
<td>ns</td>
<td></td>
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<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>

Palliative HAI and secondary liver resection, same experience in the US

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 Chemotherapy</th>
<th>Control</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: \( \chi^2 = 9.27, \text{df} = 6 \) (P = 0.16); \( I^2 = 35\% \)

Test for overall effect: \( Z = 0.83 \) (P = 0.41)

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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*

**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

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

**HAI oxaliplatin + iv LV5FU2**

n = 114
Use of IAHC??

Diagnosis of LMCRC

Resectables immediately or secondary

Neoadjuvant Chemotherapy

Surgery

Resectable limit/Potentially Resectables

Non resectables

First line

Second line

3rd line

4th line

IAHC

PACHA

OSCAR

SULTAN

IAH

J Taieb - M Ducreux
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 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
  - 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>No.</td>
<td>%</td>
<td>No</td>
</tr>
<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>All progressions considered as events</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>Patients with treatment change censored at the time of change</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>TTP, median, months</td>
<td>2.1</td>
<td>10.0</td>
<td>0.92</td>
<td>0.47 to 1.78</td>
<td>.80</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
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: 0.69 (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 Moschandreas, 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 chemotherapy for advanced disease
- Fit for combination therapy and selective internal radiation therapy (SIRT)

**Stratified by**
- Presence of extrahepatic metastases
- Degree of liver involvement
- Intended use of biologic agent
- Institution

**Randomised**
1:1
n = 1,103

- mFOLFOX6/OxMdG ± biologic
  - n = 554
- mFOLFOX6/OxMdG ± bevacizumab
  - 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><strong>Treatment protocol</strong></td>
<td><strong>FOXFIRE</strong></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. JMRI 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>
Italian Phase III

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

**TACE**

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

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>Treatment</th>
<th>OS (m)</th>
<th>ORR (%)</th>
<th>PFS (m)</th>
<th>Early (G2/3) (%)</th>
<th>Late (G2) (%)</th>
<th>Increase in QOL (%)</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEBIRI (n = 34)</td>
<td>22</td>
<td>69</td>
<td>7</td>
<td>70**</td>
<td>20</td>
<td>60</td>
<td>5000 € (2 Deb)</td>
</tr>
<tr>
<td>FOLFIRI (n = 35)</td>
<td>15</td>
<td>20</td>
<td>4</td>
<td>25</td>
<td>80</td>
<td>22</td>
<td>18000 € (8 CTx)</td>
</tr>
</tbody>
</table>

**PFS**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cumulative survival</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEBIRI</td>
<td><img src="image1" alt="Graph" /></td>
<td>0.03</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td><img src="image2" alt="Graph" /></td>
<td>0.006</td>
</tr>
</tbody>
</table>

**Toxicity**

*Edmonton score compared to baseline*

**pain, vomiting, fatigue**

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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)