The following summarises the key data within the broad clinical platform supporting the use of SIR-Spheres Y-90 resin microspheres in the treatment of liver metastases arising from colorectal cancer (mCRC) and provides results from various chemotherapy regimens as a comparative reference point.

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>n</th>
<th>Treatment</th>
<th>Cohort</th>
<th>ORR</th>
<th>SD</th>
<th>Median TTP(^9) or PFS(^*)</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray(^1)</td>
<td>74</td>
<td>SIR-Spheres(^1) + FUDR HAC vs. FUDR HAC</td>
<td>LO</td>
<td>44.0%(^{39})</td>
<td>8.3%</td>
<td>15.9 months(^{46})</td>
<td>39.0% at 2 yr</td>
</tr>
<tr>
<td>van Hazel(^2,3)</td>
<td>21</td>
<td>SIR-Spheres(^4) + 5FU/LV vs. 5FU/LV</td>
<td>LD</td>
<td>90.1%(^*)</td>
<td>0%</td>
<td>18.6 months(^4)</td>
<td>29.4 months</td>
</tr>
<tr>
<td>Sharma(^4)</td>
<td>20</td>
<td>SIR-Spheres(^4) + FOLFOX4</td>
<td>LD</td>
<td>90.0%</td>
<td>10.0%</td>
<td>9.3 months(^*)</td>
<td>14.2 months</td>
</tr>
<tr>
<td>Kosmider(^5)</td>
<td>19(^*)</td>
<td>SIR-Spheres(^4) + FOLFOX4 or 5FU/LV vs. 5FU/LV</td>
<td>LD</td>
<td>84.0%</td>
<td>5.0%</td>
<td>10.4 months(^*)</td>
<td>29.4 months</td>
</tr>
<tr>
<td>Tie(^6)</td>
<td>31(^*)</td>
<td>SIR-Spheres(^4) + FOLFOX4 or 5FU/LV vs. 5FU/LV</td>
<td>LD</td>
<td>91.0%</td>
<td>9.0%</td>
<td>13.2 months(^*)</td>
<td>30.7 months</td>
</tr>
<tr>
<td>van Hazel(^7) (SIRFLOX)</td>
<td>530</td>
<td>SIR-Spheres(^4) + mFOLFOX6 (±bev) vs. mFOLFOX6 (±bev)</td>
<td>LD</td>
<td>76.4%</td>
<td>68.1%</td>
<td>10.7 months(^*)</td>
<td>16.4 months(^*)</td>
</tr>
<tr>
<td>Sangro(^8)</td>
<td>23(^*)</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>6.3(^{35})/11.2(^{35}) months</td>
<td>16.8(^{35})/23.6(^{35}) months</td>
</tr>
<tr>
<td><strong>Consolidation of First-Line</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lim(^9)</td>
<td>30</td>
<td>SIR-Spheres(^1) (+ 5FU)(^{70%})</td>
<td>LD</td>
<td>33.0%</td>
<td>27.0%</td>
<td>5.3 months(^*)</td>
<td>nr</td>
</tr>
<tr>
<td>van Hazel(^10)</td>
<td>25</td>
<td>SIR-Spheres(^4) + irinotecan</td>
<td>LD</td>
<td>48.0%</td>
<td>39.0%</td>
<td>6.0 months(^*)</td>
<td>12.2 months</td>
</tr>
<tr>
<td>Narsinh(^11) (INSIRT)</td>
<td>10</td>
<td>SIR-Spheres(^1) &gt; FOLFIRI FOLFIRI (historical control)</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>10.2 months(^*)</td>
<td>17.6 months</td>
</tr>
<tr>
<td>Kennedy(^12) (MORE)</td>
<td>206(^*)</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>13.0 months</td>
</tr>
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</table>

**Second-Line**

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>n</th>
<th>Treatment</th>
<th>Cohort</th>
<th>ORR</th>
<th>SD</th>
<th>Median TTP(^9) or PFS(^*)</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim(^9)</td>
<td>30</td>
<td>SIR-Spheres(^1) (+ 5FU)(^{70%})</td>
<td>LD</td>
<td>33.0%</td>
<td>27.0%</td>
<td>5.3 months(^*)</td>
<td>nr</td>
</tr>
<tr>
<td>van Hazel(^10)</td>
<td>25</td>
<td>SIR-Spheres(^4) + irinotecan</td>
<td>LD</td>
<td>48.0%</td>
<td>39.0%</td>
<td>6.0 months(^*)</td>
<td>12.2 months</td>
</tr>
<tr>
<td>Narsinh(^11) (INSIRT)</td>
<td>10</td>
<td>SIR-Spheres(^1) &gt; FOLFIRI FOLFIRI (historical control)</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>10.2 months(^*)</td>
<td>17.6 months</td>
</tr>
<tr>
<td>Kennedy(^12) (MORE)</td>
<td>206(^*)</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>13.0 months</td>
</tr>
</tbody>
</table>

phase II/III studies 2nd-line systemic therapies

- irinotecan + cetuximab\(^{13-16}\) 16.0–27.0% 3.2–4.0 months\(^*\) 8.6–10.7 months
- FOLFIRI + aflibercept\(^17\) 20.0% 6.9 months\(^*\) 13.5 months
- FOLFIRI + ramucirumab\(^18\) 13.0% 5.7 months\(^*\) 13.3 months

**Key:** ORR: objective response rate (complete response + partial response) by RECIST unless indicated \(^*\) WHO criteria; SD: stable disease; TTP: time to progression; PFS: progression-free survival; \(^9\) TTP or PFS in the liver; \(^*\) SIR-Spheres Y-90 resin microspheres; LO: liver-only disease; LD: liver-dominant disease; \(^{90.1\%}\) by First Integrated Response, 72.7% by Best Confirmed Response; HR: hazard ratio; nr: not reported; \(^*\) retrospective study; \(^{±bev}\): bevacizumab allowed at investigator's discretion, per institutional practice; \(^{±}\) from date of SIRT; \(^*\) from first course of chemotherapy; BSC: best supportive care; \(^\text{DCR}\) disease control rate; \(^{\text{CChoi}\, \text{criteria}}\)
### Salvage Therapy of Treatment-Refractory Disease

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>n</th>
<th>Treatment</th>
<th>Cohort</th>
<th>ORR</th>
<th>SD</th>
<th>Median TTP or PFS</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hendliz19</td>
<td>44</td>
<td>SIR-Spheres(^1) + 5FU vs. SFU (≥ SIR-Spheres(^1) at PD)</td>
<td>LO</td>
<td>10.0%</td>
<td>76.0%</td>
<td>5.5 months(^{26})</td>
<td>HR: 0.38 (P = 0.003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LO</td>
<td>0%</td>
<td>35.0%</td>
<td>2.1 months(^{11})</td>
<td>HR: 0.26 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Seidensticker(10)</td>
<td>29</td>
<td>SIR-Spheres(^1) vs. BSC (matched pairs)</td>
<td>LD</td>
<td>41.4%</td>
<td>17.2%</td>
<td>5.5 months(^{11})</td>
<td>HR: 0.26 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>vs. conventional therapy or BSC</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>2.1 months(^{11})</td>
<td>HR: 0.26 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Bester(^{21})</td>
<td>224</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>11.9 months (P = 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>6.6 months (P = 0.0001)</td>
</tr>
<tr>
<td>Cosimelli(^{22})</td>
<td>50</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>24.0%</td>
<td>24.0%</td>
<td>4.0 months(^{11})</td>
<td>HR: 0.26 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Sofocleous(^{23})</td>
<td>19</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>5.0%</td>
<td>53.0%</td>
<td>2.0 months(^{11})</td>
<td>HR: 0.26 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Kennedy(^{12})</td>
<td>184</td>
<td>SIR-Spheres(^1) 3rd-line (MORE)</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>9.0 months (P = 0.667)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>8.1 months (P &lt; 0.001)</td>
</tr>
<tr>
<td>Sofocleous(^{24})</td>
<td>53</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>7.0%</td>
<td>61.0%</td>
<td>4.7 months(^{11})</td>
<td>HR: 0.26 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Leoni(^{25})</td>
<td>51</td>
<td>SIR-Spheres(^1) (+ FUDR HAC(^{23}))</td>
<td>LD</td>
<td>12.9%</td>
<td>64.5%</td>
<td>nr</td>
<td>10.2 months (P = 0.41)</td>
</tr>
<tr>
<td>Nace(^{26})</td>
<td>51</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>53.0%</td>
<td>nr</td>
<td>nr</td>
<td>8.0 months (P = 0.0001)</td>
</tr>
<tr>
<td>Cianni(^{27})</td>
<td>41</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>46.0%</td>
<td>36.0%</td>
<td>9.3 months(^{11})</td>
<td>HR: 0.26 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Jakobs(^{28})</td>
<td>41</td>
<td>SIR-Spheres(^1)</td>
<td>LD</td>
<td>17.0%</td>
<td>61.0%</td>
<td>5.9 months(^{11})</td>
<td>HR: 0.26 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Kennedy(^{29})</td>
<td>208</td>
<td>SIR-Spheres(^1) responders non-responders &amp; historical controls</td>
<td>LD</td>
<td>35.5%</td>
<td>55.0%</td>
<td>nr</td>
<td>10.5 months (P = 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LO/LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>4.5 months (P = 0.0001)</td>
</tr>
<tr>
<td>Tohme(^{30})</td>
<td>63</td>
<td>SIR-Spheres(^1) in &lt;70 years</td>
<td>LO/LD</td>
<td>12.2%</td>
<td>53.6%</td>
<td>nr</td>
<td>8.4 months (P = 0.41)</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>SIR-Spheres(^1) in ≥70 years</td>
<td>LO/LD</td>
<td>11.8%</td>
<td>64.7%</td>
<td>nr</td>
<td>8.2 months (P = 0.0001)</td>
</tr>
<tr>
<td>Sabet(^{31})</td>
<td>51</td>
<td>SIR-Spheres(^1) in &gt; PET PR SIR-Spheres(^1) in &gt; PET no PR</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>10.0 months (P = 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LO</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>4.0 months (P = 0.0001)</td>
</tr>
<tr>
<td>Lahti(^{32})</td>
<td>59</td>
<td>SIR-Spheres(^1)KRAS(^{\text{wild-type}})</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>9.5 months (P = 0.041)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>SIR-Spheres(^1)KRAS(^{\text{mutant}})</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>4.8 months (P = 0.041)</td>
</tr>
<tr>
<td>Golfier(^{33})</td>
<td>52</td>
<td>SIR-Spheres(^1)</td>
<td>LO/LD</td>
<td>59.0%</td>
<td>64.5%</td>
<td>nr</td>
<td>11.0 months (P = 0.0001)</td>
</tr>
<tr>
<td>Maleux(^{34})</td>
<td>71</td>
<td>SIR-Spheres(^1)</td>
<td>LO/LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>8.0 months (P = 0.0001)</td>
</tr>
</tbody>
</table>

#### phase III studies systemic therapies\(^{35,36}\)

| Regorafenib | LO/LD | 1.0% | 19.0% | 1.9 months\(^{11}\) | 6.4 months \(P = 0.0052\) |
| 255 BSC     |       | 0.4% | 15.0% | 1.7 months\(^{11}\) | 5.0 months \(P = 0.0052\) |
| 534 TAS-102 |       | 1.6% | 44.0% | 2.0 months\(^{11}\) | 7.1 months \(P = 0.0001\) |
| 266 BSC     |       | 0.4% | 16.0% | 1.7 months\(^{11}\) | 5.3 months \(P = 0.0001\) |

**Key:** ORR: objective response rate (complete response + partial response) by RECIST unless indicated \(^{1}\); SD: stable disease; TTP: time to progression; PFS: progression-free survival; \(\geq\): TTP or PFS in the liver; SIR-Spheres: Y-90 resin microspheres; LO: liver-only disease; LD: liver-dominant disease; HR: hazard ratio; sr: not reported; \(*\): retrospective study; \(\geq\): from date of SIRT; BSC: best supportive care; \(\text{DCR control rate; CChoi criteria}\)
Studies of SIR-Spheres Y-90 resin microspheres in Combination with First-line Chemotherapy

The combination of SIR-Spheres Y-90 resin microspheres with first-line chemotherapy have reported impressive results in three randomised controlled trials (RCTs) and a dose-escalation study,\textsuperscript{1–4} as well as in retrospective analyses including consolidation therapy.\textsuperscript{5,6,8}

RCT of SIR-Spheres Y-90 resin microspheres + hepatic arterial chemotherapy vs. HAC alone at first-line

A RCT by Gray et al. of SIR-Spheres Y-90 resin microspheres plus hepatic arterial chemotherapy (HAC) using fluorouridine compared to HAC alone in 74 patients with mCRC was halted prematurely after the FDA stated that treatment-related response and time to progression were acceptable criteria for registration. The predominately first-line study (14.3% of patients had received prior chemotherapy for their liver metastases) showed:\textsuperscript{1}

- patients (mean age 60 years) had WHO performance status 0–2 and metastases limited to the liver and the lymph nodes of the porta hepatis;\textsuperscript{1}
- a significantly higher objective response rate for patients receiving SIR-Spheres Y-90 resin microspheres + HAC compared to HAC alone by both WHO criteria confirmed at three months (44.4% vs. 17.6%; \(P = 0.01\)) and ±50% reduction in elevated CEA values (72.2% vs. 47.1%; \(P = 0.004\));\textsuperscript{1}
- a significantly longer median time to progression (TTP) of disease in the liver for patients receiving SIR-Spheres Y-90 resin microspheres + HAC compared to HAC alone (15.9 vs. 9.7 months; \(P = 0.001\)) and a trend for a survival advantage in those patients surviving more than 15.0 months (\(P = 0.06\));\textsuperscript{1}
- the risk of death from progression of liver metastases was 3.1 times higher for patients in the HAC-only arm (95% CI 1.1–8.8; \(P = 0.03\));\textsuperscript{1}
- no difference in the rate of grade 3 or 4 toxicity events, with 23 in each arm;\textsuperscript{1}
- no major adverse impact on quality of life by the addition of SIR-Spheres Y-90 resin microspheres to HAC, with improved quality of life in both arms;\textsuperscript{1}
- the authors concluded that adding a single administration of SIR-Spheres Y-90 resin microspheres to hepatic arterial chemotherapy significantly increased treatment effectiveness measured by tumour response and time to disease progression.\textsuperscript{1}

RCT of SIR-Spheres Y-90 resin microspheres + 5FU/LV first-line chemotherapy vs. 5FU/LV alone

A second RCT by van Hazel and colleagues, comparing SIR-Spheres Y-90 resin microspheres plus 5FU/LV versus 5FU/LV alone in the first-line treatment of 21 patients with liver metastases from CRC demonstrated significant benefits in favour of SIR-Spheres Y-90 resin microspheres.\textsuperscript{2} This study reported:

- patients (mean age 64.5 years) had WHO performance status 0–2 with 24% having extra-hepatic disease in either the lung or peritoneum;\textsuperscript{2}
- all patients had multiple bilobar metastases and were reviewed by a surgical oncology unit to confirm that they were not amenable to either resection or ablation;\textsuperscript{2}
- significantly greater ORR for patients receiving the combination of SIR-Spheres Y-90 resin microspheres + 5FU/LV (ORR: 90.1% using First Integrated Response, 72.7% using Best Confirmed Response vs. 0% by RECIST; \(P < 0.001\));\textsuperscript{2}
- significantly longer median TTP for the combination of SIR-Spheres Y-90 resin microspheres + 5FU/LV (18.6 vs. 3.6 months; \(P < 0.0005\)), with patients in the combination arm able to receive chemotherapy for a longer period (median 8.1 vs. 3.8 cycles; \(P = 0.03\));\textsuperscript{2}
- significantly longer median overall survival for SIR-Spheres Y-90 resin microspheres + 5FU/LV compared to 5FU/LV alone (29.4 vs. 12.8 months; HR 0.33, 95% CI 0.12–0.91; \(P = 0.025\));\textsuperscript{2}
- there were more grade 3/4 toxicities in patients receiving the combination of SIR-Spheres Y-90 resin microspheres + 5FU/LV, although the investigators considered that this was largely due to the greater period that these patients received protocol treatment;\textsuperscript{2}
- the health-related quality of life (HRQoL) of patients was not compromised by the addition of SIR-Spheres Y-90 resin microspheres and that compared to 5FU/LV, patients receiving SIR-Spheres Y-90 resin microspheres + 5FU/LV showed a significant improvement in HRQoL at three months (\(P = 0.03\)). This improvement was sustained at six, 12, 15 and 24 months;\textsuperscript{2,3}
- the investigators concluded that this small RCT demonstrated that the addition of a single administration of SIR-Spheres Y-90 resin microspheres to 5FU/LV systemic chemotherapy increased treatment-related response, time to progression, quality of life and survival with acceptable toxicity.\textsuperscript{2,3}
Dose-escalation study of SIR-Spheres Y-90 resin microspheres + FOLFOX4 first-line chemotherapy

The results of a dose-escalation study by Sharma et al. combining SIR-Spheres Y-90 resin microspheres with first-line FOLFOX4 (oxaliplatin + 5FU/LV) chemotherapy in 20 mCRC patients demonstrated:4

- patients (median age 59 years) had WHO performance status 0–1, 35% had their primary disease in situ and 65% had extra-hepatic disease to the lung, lymph nodes, peritoneum and/or spleen;4
- a 90% response rate by RECIST, together with a disease control rate of 100%.4 No patients reported progressive disease;4
- three patients (15%) were down-staged and two (10%) were surgically resected;4
- decreased serum CEA levels were seen in all patients with a baseline elevation, from a median of 470 ng/mL pre-treatment to 9 ng/mL at six months;4
- median progression-free survival (PFS) was 9.3 months in all patients and 14.2 months in those with liver-only disease at entry. Median TTP in the liver was 12.3 months and 16.0 months for those with liver-only disease at entry;4,37
- at the time of reporting, five patients remained alive and four had not progressed in the liver at 15–18 months from receiving SIR-Spheres Y-90 resin microspheres;4
- the authors noted that the combination of SIR-Spheres Y-90 resin microspheres with first-line FOLFOX4 was generally well tolerated.4 The dose-limiting toxicity was neutropenia, recorded in 12 patients, and the maximum tolerated dose for the first three cycles of oxaliplatin was 60 mg/m²;4
- the authors concluded that although the sample size was small and therefore must be interpreted with caution, these data were impressive and compare favourably to phase II/III data on FOLFOX4,4 which report 32–59% ORR and median TTP or PFS of 7.6–9.0 months.38–41

SIR-Spheres Y-90 resin microspheres combined with first-line systemic chemotherapy

A retrospective analysis by Kosmider et al. of SIR-Spheres Y-90 resin microspheres in combination with chemotherapy (5FU/LV or FOLFOX) as first-line treatment in 19 patients with unresectable CRC liver metastases demonstrated:3

- patients (median age 62 years) had ECOG performance status 0–1. Most patients (95%) presented with synchronous metastases, good performance status (ECOG 0: 53%) with a median of 40% liver involvement (range 25–65%); 26% had extra-hepatic metastases;3
- chemotherapy selection was at clinician discretion and according to local protocols; 12 of the 19 patients (63%) received FOLFOX chemotherapy and seven patients (37%) received 5FU/LV;3
- two patients (11%) with disease confined to the liver showed a complete response, 14 (74%) had a partial response and one (5%) had stable disease;3
- median PFS was 10.4 months, with a trend for improved PFS in patients with liver-confined disease (10.7 vs. 3.6 months; \( P = 0.09 \));3
- median overall survival for all patients was 29.4 months. When patients were stratified by the presence or absence of extra-hepatic disease at diagnosis, overall survival was significantly longer for those with liver-only disease (median 37.8 vs. 13.4 months; \( P = 0.03 \)). One patient had been disease-free per RECIST for more than six years, and two others remained in partial remission after more than three years of follow-up;3
- the majority of adverse events that occurred in the first month were abdominal pain (seven patients; 37%) and fatigue (10 patients; 53%). One patient who received FOLFOX chemotherapy with full-dose oxaliplatin (85 mg/m²) experienced an episode of febrile neutropenia within the first three cycles. No other patients had grade 3/4 toxicity. The most serious adverse event was a treatment-related death from hepatic failure, presumed to represent radiation hepatitis, two months after treatment with SIRT and FOLFOX. One patient with gastroduodenitis at 12 weeks was diagnosed with a perforated duodenal ulcer; this patient had not undergone embolisation of the GDA or RGA before radioembolisation;3
- the authors concluded that the present early series provides some valuable insights into the potential of radioembolisation with SIR-Spheres Y-90 resin microspheres when used in combination with chemotherapy for the first-line treatment of patients with liver-dominant metastases from colorectal cancer. Patients with liver-only disease derived the greatest benefit.3

The SIRFLOX study: an international, multi-centre, open-label, Phase III RCT comparing first-line mFOLFOX6 (±bev) vs. mFOLFOX6 (±bev) + SIR-Spheres Y-90 resin microspheres

SIRFLOX is the largest randomised interventional radiology study ever conducted in oncology. The investigators reported:7

- n=530 (n=263 arm A; n=267 arm B) chemotherapy-naive patients with non-resectable, liver-only or liver-dominant (liver plus lung and/or lymph node metastases) mCRC were randomised to receive either mFOLFOX6 (±bev) (arm A) or mFOLFOX6 (±bev) + SIR-Spheres Y-90 resin microspheres (arm B); bevacizumab (bev) was allowed at investigator’s discretion, per institutional practice;7
• a majority of patients had poor prognostic factors at baseline; 40% had extra-hepatic metastases in both arms, 46% and 45% had the primary tumour in situ, and 89% and 90% had synchronous metastases in arm A and arm B, respectively;7
• median overall PFS – the primary endpoint of the study – was 12.2 vs. 10.7 months in arm A vs. B, respectively (HR: 0.93; 95% CI 0.77–1.12; P = 0.429);7
• median Liver PFS was 12.6 vs. 20.5 months in arm A vs. B (HR: 0.69; 95% CI 0.55–0.90; P = 0.002) by competing risk analysis; SIR-Spheres Y-90 resin microspheres significantly extended PFS in the liver with a 31% risk reduction of progression in the liver;7
• median Liver PFS was 12.4 vs. 21.1 months in arm A vs. B (HR: 0.64; 95% CI 0.48–0.86; P = 0.003) for patients with liver-only metastases, and 12.6 vs. 16.7 months (HR: 0.77, 95% CI 0.54–1.09; P = 0.147) for those with liver and extra-hepatic metastases;42
• median Liver PFS was 10.6 vs. 18.9 months in arm A vs. B (HR: 0.69; 95% CI 0.50–0.96; P = 0.028) for patients with ITT for no bevacizumab, and 12.7 vs. 21.0 months (HR: 0.69, 95% CI 0.50–0.94; P = 0.018) for those with ITT to receive bevacizumab; SIR-Spheres Y-90 resin microspheres significantly extend PFS in the liver with a 31% reduction in risk of progression in the liver, independent of bevacizumab;42
• ORR (PR + CR) was 68.1% vs. 76.4% in arm A vs. B, respectively (P = 0.113); hepatic ORR was 68.8% vs. 78.7% in arm A vs. B (P = 0.042), including a complete response (CR) rate of 1.9% vs. 6.0% (P = 0.02);7
• the liver resection rate was 13.7% vs. 14.2% in arm A vs. B (P = 0.857);7
• all-causality grade ≥3 adverse events were noted in 73.3% of patients in arm A vs. B, respectively; grade 5 events occurred in 1.9% vs. 3.7% in arm A vs. B (NS);7
• the investigators concluded that the addition of SIR-Spheres Y-90 resin microspheres to standard chemotherapy failed to improve overall PFS. However, median liver PFS was significantly extended. The addition of SIR-Spheres Y-90 resin microspheres was associated with acceptable toxicity.7

Consolidation therapy using SIR-Spheres Y-90 resin microspheres following first-line chemotherapy

A retrospective analysis by Sangro et al. of SIR-Spheres Y-90 resin microspheres in 23 patients with liver-dominant mCRC who were deemed to still be unresectable 12–26 weeks (median 21 weeks) after the start of first-line chemotherapy showed:8

• patients (median age 60.2 years) had received oxaliplatin (100%), 5FU (8.7%) or capcitabine (91.3%), plus cetuximab (60.9%), irinotecan (21.7%) or bevacizumab (8.7%), with many (43.5%) having received hepatic arterial chemotherapy. Most patients had bilobar disease (82.6%) and extra-hepatic metastases (56.5%) in the lymph nodes, lung and/or peritoneum;8
• the best response to chemotherapy was partial response or stable disease (91.3%), or progressive disease (8.7%);8
• following treatment with SIR-Spheres Y-90 resin microspheres, three patients (13%) had their tumours sufficiently down-sized to enable surgical resection ± RFA. These patients were censored at time of surgery for the PFS and survival analyses;8
• patients received further chemotherapy either upon progression or as maintenance therapy, with 14 patients receiving no chemotherapy in the three-month period following SIR-Spheres Y-90 resin microspheres;8
• median PFS was 6.3 months post-SIRT and 11.2 months from the first course of chemotherapy;8
• median overall survival was 16.8 months post-SIRT and 23.6 months from the first course of chemotherapy;8
• no grade 3 or 4 acute adverse events were recorded following treatment. There was a statistically significant but clinically irrelevant increase in bilirubin levels peaking at two to three months post-SIRT. Four patients developed grade 1–2 radiation induced liver disease, defined by peak bilirubin >2 mg/dl and ascites two to three months post-SIRT;8
• the investigators concluded that consolidation using SIR-Spheres Y-90 resin microspheres after first-line treatment is a safe procedure that may reduce the rate of liver progression, further extend the proportion of patients receiving surgical resection and help provide long-term survival.8
**Studies of SIR-Spheres Y-90 resin microspheres as Second-Line Therapy**

In patients who have failed at least first-line chemotherapy, encouraging results have been reported with SIR-Spheres Y-90 resin microspheres alone, or combined with chemotherapy.9–12

**Dose-escalation study of SIR-Spheres Y-90 resin microspheres + irinotecan second-line chemotherapy**

A multi-centre dose-escalation study by van Hazel et al. combining SIR-Spheres Y-90 resin microspheres with irinotecan in 25 patients failing prior chemotherapy showed:10

- patients (mean age 59 years) had all failed at least first-line chemotherapy, with 32% having also failed second- or third-line regimens, and 60% having failed oxaliplatin-based regimens. Half of patients (52%) had liver-only metastases, with the remainder having extra-hepatic disease in the lymph nodes (12%) or lungs (36%);10
- an objective response rate of 48% by RECIST, with a disease control rate of 87%;10
- median serum CEA decreased by 82% at three months post-SIRT;10
- the median PFS was 6.0 months (range 1.6–11.4), and the PFS in the liver was 9.2 months (1.6–25.8);10
- median overall survival of 12.2 months (range 2.8–60+ months), with three patients still alive at the time of reporting;10
- these data compare favourably to phase II/III studies on irinotecan-based regimens;13–16
- the authors noted that the combination of SIR-Spheres Y-90 resin microspheres with irinotecan had a safety profile equivalent to single-agent irinotecan in this disease setting, with significantly less myelosuppression than that reported in the dose-escalation study with FOLFOX;4,10
- the authors concluded that SIR-Spheres Y-90 resin microspheres in combination with weekly irinotecan at 100 mg/m² demonstrated an acceptable toxicity profile and promising efficacy.10

**Studies of SIR-Spheres Y-90 resin microspheres in Chemorefractory Disease**

In heavily pre-treated, chemorefractory patients who have failed standard of care, SIR-Spheres Y-90 resin microspheres demonstrated consistent and clinically meaningful results in a RCT and two comparative studies, as well as in retrospective analyses of routine clinical practice.12,19–34

**RCT of SIR-Spheres Y-90 resin microspheres + 5FU chemotherapy vs. 5FU alone**

In a multi-centre RCT conducted in Belgium by Hendliz et al., 44 patients with CRC liver metastases that were refractory to or could not tolerate multiple prior lines of standard-of-care chemotherapy including oxaliplatin and irinotecan were randomised to either SIR-Spheres Y-90 resin microspheres plus infusional 5FU or 5FU alone.19 On disease progression, patients in the control arm were reassessed for cross-over to salvage therapy with SIR-Spheres Y-90 resin microspheres. The investigators reported:

- all patients (median age 62; range 45–91) had liver-only metastases and were balanced between the two arms without significant differences;19
- disease control rate (PR + SD) was significantly higher in patients receiving SIR-Spheres Y-90 resin microspheres + 5FU compared to 5FU alone (86% vs. 35%, respectively; \( P = 0.001 \)).19 Despite no previous objective response to both FOLFOX and FOLFIRI chemotherapy, one patient receiving SIR-Spheres Y-90 resin microspheres + 5FU had a sufficiently large reduction in tumour size to permit potentially curative surgical resection of the remaining disease;44
- median TTP in the liver – the primary endpoint of the study – was significantly increased in the SIR-Spheres Y-90 resin microspheres + 5FU arm compared to the 5FU-only arm (5.5 vs. 2.1 months, respectively; HR 0.38, 95% CI 0.20–0.72; \( P = 0.003 \));19
- median TTP anywhere in the body was also significantly longer for patients receiving SIR-Spheres Y-90 resin microspheres + 5FU compared to 5FU alone (4.5 vs. 2.1 months, respectively; HR 0.51, 95% CI 0.28–0.94; \( P = 0.03 \));19
- following progression of disease, 10 patients (43.5%) in the 5FU-only arm subsequently crossed over to receive SIR-Spheres Y-90 resin microspheres alone as salvage therapy and so overall survival was extended in both treatment arms by the targeted treatment of liver tumours.19 Overall, there was 2.5 months’ difference in the median survival (10.0 vs. 7.3 months) between the combination and 5FU-only arms, respectively (HR 0.92; \( P = 0.80 \)).19
• treatment with SIR-Spheres Y-90 resin microspheres + 5FU was well tolerated, with more patients experiencing a serious adverse event in the 5FU-only control arm (six vs. one, respectively; \(P = 0.10\)). The investigators noted that this increase was probably due to the lower efficacy of 5FU alone and more rapidly progressing disease.19
• the authors concluded that SIR-Spheres Y-90 resin microspheres combined with systemic 5FU significantly prolongs both liver and overall TTP, compared with 5FU alone in a cohort of patients with liver-only disease at the time of randomisation, and that toxicities with the combination remained very low and easily manageable. The investigators recommended that SIRT/radioembolisation using SIR-Spheres Y-90 resin microspheres should be considered as a valid therapeutic option in patients with liver-limited chemotherapy refractory mCRC.19

**Comparative study of SIR-Spheres Y-90 resin microspheres vs. a matched-pair cohort receiving best supportive care**

A retrospective study was performed by Seidensticker *et al.* to investigate the efficacy and safety of SIR-Spheres Y-90 resin microspheres as salvage therapy in 29 heavily pre-treated patients with extensive (≥20% liver involvement) and progressive liver-dominant disease which were followed prospectively, compared to 29 matched-pair control patients who received best supportive care (BSC).20

Control patients were matched by tumour burden, synchronous vs. metachronous metastases, ALP increase and CEA >200 U/mL.20 The results showed:

- 58 patients’ (mean age 61.6 years) characteristics were well balanced between the SIR-Spheres Y-90 resin microspheres and BSC cohorts, with extensive liver tumour involvement: median 30% (range 20–50%) vs. 25% (10–75%), respectively. Patients in each cohort received a median of three (2–6) prior lines of chemotherapy;20
- the two cohorts were matched on all four criteria in 16 pairs (55.2%), with the remainder matching by three and two criteria (37.9% and 6.9%, respectively);20
- a partial response was observed in 12 patients (41.4%), with stable disease in a further five patients (17.2%);20
- median PFS was 5.5 months in patients receiving SIR-Spheres Y-90 resin microspheres, compared with 2.1 months in the BSC cohort;20
- median overall survival was significantly longer for the patients receiving SIR-Spheres Y-90 resin microspheres compared with BSC (8.3 vs. 3.5 months; HR 0.26, 95% CI 0.15–0.48; \(P < 0.001\)). This benefit was clearly evident at three months (97% vs. 59% survival) and was sustained through 12-months follow up (24% vs. 0% survival);20
- adverse events following SIR-Spheres Y-90 resin microspheres included grade 1–2 fatigue (69%), grade 1 abdominal pain/nausea (48.3%) and three patients (10.3%) experienced grade 2 GI ulcers. Three cases (10.3%) of radiation-induced liver disease were medically managed and not considered life-threatening (median survival 9.8 months; range 9.0–16.6);20
- a multivariate Cox proportional hazard model analysis revealed that treatment with SIR-Spheres Y-90 resin microspheres was the only significant predictor for prolonged survival (HR 0.30; 95% CI 0.16–0.55; \(P < 0.001\)), whereas the extent of liver involvement was associated with an increased risk of death (HR 1.03; 95% CI 1.0–1.06; \(P = 0.028\));20
- the investigators concluded that SIR-Spheres Y-90 resin microspheres in addition to BSC provides substantial clinical benefit as evidenced by significantly prolonged overall survival compared with BSC alone in a well-matched cohort of patients with extensive liver-dominant treatment-refractory disease for whom there are limited treatment options.20

**Comparative study of SIR-Spheres Y-90 resin microspheres vs. control patients receiving standard care**

A retrospective study by Bester *et al.* analysed the survival outcomes for patients receiving SIR-Spheres Y-90 resin microspheres compared to control patients referred back to their treating physician for conventional therapy or best supportive care in 339 patients with unresectable chemotherapy refractory liver-dominant metastases, including 253 patients with mCRC:21

- the study excluded patients with extensive extrahepatic metastases, ECOG performance status score >2, excessive hepatic tumour burden (>75%), and/or compromised residual liver function. This ensured that the standard-care control group, which comprised patients unsuitable for SIRT due to potential for non-target delivery to the GI tract or lungs, or reasons relating to patient consent (e.g. refusal or other treatment option chosen), was unlikely to represent patients with more advanced disease;21
- patients with mCRC presented with good performance status (ECOG 0, 85%), with bilobar disease (87%) and typically 0–25% tumour burden in the liver, although 38% had limited extrahepatic disease;21
- the investigators reported that overall survival was significantly prolonged in 224 patients with chemotherapy refractory mCRC receiving SIR-Spheres Y-90 resin microspheres compared with 29 control mCRC patients receiving standard care (median 11.9 vs. 6.6 months; HR 0.50; \(P < 0.001\));21
- in a multivariate analysis, SIRT using SIR-Spheres Y-90 resin microspheres was the only significant predictor for prolonged survival (HR 0.57; \(P = 0.002\)).21
• treatment was well tolerated, with minor adverse events at the time of SIRT (grade 1 abdominal pain, nausea/vomiting) in 22% of patients. Grade 1 abdominal pain (18%) and lethargy (12%) was reported in the first week following SIRT, with 1.8% grade 2 gastritis, 0.6% grade 2 gallbladder complications, 0.6% grade 2 ulceration and 0.3% mild (grade 2) radiation-induced liver disease. At the 3-month follow-up, there were 3.2% grade 2/3 GI ulcerations, 2.9% radiation-induced liver disease and 1.8% gallbladder complications. These adverse events were all medically managed, with no deaths within the 3-month follow-up.21
• the authors concluded that SIRT using SIR-Spheres Y-90 resin microspheres is an effective and safe treatment for patients with chemotherapy-refractory liver metastases and improves overall survival in a select population compared with standard care alone.21

Data on an extended cohort of 302 mCRC patients treated with SIR-Spheres Y-90 resin microspheres published by Saxena et al. showed the following:25

• treatment response in all 302 patients was: CR in two patients (1%), PR in 111 patients (37%), SD in 96 patients (32%), and PD in 84 patients (28%); in the 159 patients who underwent one previous line of chemotherapy, CR/PR was observed in 69 patients (43%), SD in 46 (29%), and PD in 41 (26%); in the 91 patients who underwent two previous lines of chemotherapy, CR/PR was observed in 32 patients (35%), SD in 34 (37%), and PD in 22 (24%); in the 52 patients who underwent three or more previous lines of chemotherapy, CR/PR was observed in 12 patients (23%), SD in 15 (29%), and PD in 21 (40%). This was significant on univariate analysis (P = 0.046);45
• median survival after the first treatment with SIR-Spheres Y-90 resin was 10.5 months with 6-month and 12-, 18-, 24-, 30-, 36-, and 60-month survival of 66, 42, 29, 21, 17, 13, and 7%, respectively;25
• in patients who underwent treatment with one previous line of chemotherapy, median survival was 12.0 months, with two previous lines of chemotherapy, median survival was 10.5 months, at least three previous lines of chemotherapy, median survival was 5.6 months. This was significant on univariate analysis (P = 0.001) and multivariate analysis (P = 0.016);45

Prospective study of SIR-Spheres Y-90 resin microspheres in salvage therapy of chemorefractory patients
A prospective multi-centre study by Cosimelli and colleagues of patients who had all failed oxaliplatin- and irinotecan-based regimens revealed:22

• 50 patients (median age 67 years) had a median WHO performance status of 0 (range 0–3), with most having extensive liver involvement (25–50%). All patients had failed ≥3 lines of chemotherapy and 76% had failed four or five lines; 22% had received prior bevacizumab;22
• the objective response rate of 24% (2% CR + 22% PR) met the pre-defined criteria for significance (P = 0.05), with two patients becoming sufficiently down-staged to plan radical surgical resection of ≥3 segments;22
• the median overall survival was 12.6 months, with a significant difference between responders (CR + PR + SD = 48%) and non-responders (PD) or unconfirmed response (16.0 vs. 8.0 months; P = 0.0006);22
• the investigators concluded that SIR-Spheres Y-90 resin microspheres “represents a promising salvage therapy for patients with unresectable, highly pre-treated colorectal liver metastases”;22
• the authors noted that the results compared favourably with phase II/III studies of chemotherapy regimens at second or subsequent lines of therapy13–15 and also reflected previous experience with SIR-Spheres Y-90 resin microspheres in retrospective studies.28,29
Dose-escalation study of SIR-Spheres Y-90 resin microspheres in patients refractory to systemic and hepatic arterial chemotherapy

A prospective phase 1 dose-escalation study by Sofocleous and colleagues in 19 patients with colon cancer liver metastases who had failed hepatic arterial (pump) and systemic chemotherapy demonstrated:23

- all patients were heavily pre-treated and had progressed after at least two prior lines of systemic chemotherapy (mean, 2.9 lines, range, 2.0–5.0 lines, 63% had at least 4 lines) and ≥1 prior line of hepatic artery chemotherapy (HAC); Extra-hepatic metastases were present in 68% of the patients. KRAS tumour status was wild type in 74% of the patients, mutant in 21% and unknown in one patient. Patients had prior liver resection in 52% of the cases;23
- treatment with SIR-Spheres Y-90 resin microspheres was administered in three escalating activity levels: the first cohort received 70%, the second 85%, and the third 100% of the calculated activity;23
- a total of 17 patients (89%) received post-SIRT chemotherapy as determined by the patients’ medical oncologist; nine (47%) received additional HAC, and four (21%) had liver ablation;23
- 11 patients (58%) responded (defined as stable disease or better) while eight (42%) had progressive disease;23
- median PFS was 2.0 months (95% CI 1.1–2.9) and median PFS in the liver was 5.2 months (range 3.3–6.4 months);23
- median overall survival was 14.9 months (95% CI 6.4–25.6);23
- of 19 patients, four experienced grade 3 toxicity (three within six weeks of SIRT), all of them developed significant disease progression; other common post-treatment side effects were grade 1–2 fatigue, abdominal pain and grade 1 fever; no dose-limiting toxicities were observed, three patients had no adverse events;23
- the authors concluded that SIRT with SIR-Spheres Y-90 resin microspheres is safe and well tolerated despite prior liver resection, multiple lines of chemotherapy, and HAC and should be considered for the management of patients with treatment-refractory liver-only or liver-dominant colorectal metastases.23

Largest US multi-centre evaluation of safety and survival of SIR-Spheres Y-90 resin microspheres in unresectable colorectal liver metastases

An investigator-initiated retrospective multi-centre study by Kennedy and colleagues analysed the outcomes following SIR-Spheres Y-90 resin microspheres in mCRC patients treated between 2002 and 2011. The study’s endpoints included safety and tolerability, tumour response and survival:12,46,47

- 606 patients (233 women; 373 men) were treated at 11 institutions in the U.S. Their mean age was 61.5 years (range, 20.8 to 91.9 years). Active extra-hepatic disease was present prior to the first SIRT procedure in 35.1% of patients;12
- patients had received a median of two prior lines of systemic chemotherapy (range, 0–6), consisting mostly of fluoropyrimidine-based treatment combined with oxaliplatin or irinotecan with or without bevacizumab (1st- or 2nd-line) or an EGFR inhibitor (typically 3rd-line);12
- after systemic chemotherapy for mCRC, 206 patients (35.3%) received SIR-Spheres Y-90 resin microspheres at 2nd-line (after one prior line of chemotherapy), 184 (31.6%) at 3rd-line (after two prior lines), and 158 patients (27.1%) at 4th-line (after three or more prior lines of chemotherapy); 30.2% had also received a prior liver-directed procedure (resection, ablation, TAE/TACE, HAI or external beam radiotherapy);12
- a median of two SIRT treatments were conducted for each patient; hospital stay was less than 24 hours in 98.7% of cases; most patients (93.2%) received SIRT as either one (49.7%) or two (43.6%) procedures, mainly targeting either the whole liver (65.7%) or right lobe (27.7%);12
- median overall survival for all 606 patients was 9.6 months (95% CI 9.0–11.1) from their first SIRT treatment, with a median follow-up of 8.6 months (0.1–77.7 months);12
- median survivals differed significantly between patients receiving SIR-Spheres Y-90 resin microspheres as a 2nd-, 3rd-, and 4th+ line of treatment after chemotherapy; median survivals (95% CI) were 13.0 months (10.5–14.6), 9.0 months (7.8–11.0), and 8.1 months (6.4–9.3), respectively (P < 0.001); survival was significantly prolonged in patients with ECOG 0 vs. ≥1 (P = 0.009);12
- RECIST 1.0 and 1.1 imaging response criteria were analysed in 195 patients and provided equivalent interpretation in the assessment of hepatic tumour following SIRT;12
- common AEs were usually mild (grade 1/2) and included: fatigue (all grades: 43.7%; grade ≥3: 5.8%), abdominal pain (39.3%; grade ≥3: 6.1%), nausea (28.4%; grade ≥3: 1.3%) and vomiting (10.6%; grade ≥3: 1.5%); Gastrointestinal ulcerations (all grades: 3.5%) was severe (grade ≥3) in 1.7% of patients and may have contributed to the death of one (0.2%) patient; there were three recorded cases among 606 (0.5%) patients of grade ≥3 radioembolisation-induced liver disease (REILD) and two further cases of grade ≥3 hepatic failure (total 5/606; 0.8%); all events occurred between 8–90 days following the first treatment and all patients subsequently died;12

Overall Survival after SIR-Spheres Stratified by Treatment Setting

![Graph showing survival distribution function](image-url)
• the comparison of safety and efficacy of SIR-Spheres Y-90 resin microspheres in elderly (≥70 years) and younger patients of the study cohort revealed that the therapy is effective and well-tolerated for both patient groups: the overall survival did not deteriorate (median 9.3 vs. 9.7 months; $P = 0.335$) and no significant increase in grade 3+ adverse events were observed in elderly patients;\textsuperscript{17}

• abnormal laboratory values prior to SIRT were associated with a poorer prognosis; compared to patients with CTCAE grade 0, those with grade ≥1 albumin showed a decreased median survival of 6.3 months ($P < 0.001$), for patients with grade ≥1 total bilirubin the median survival decreased to 3.8 months ($P < 0.001$), and for patients with grade ≥1 haemoglobin the median survival decreased to 7.6 months ($P < 0.001$);\textsuperscript{12}

• the authors conclude that even among patients who were heavily pre-treated, SIR-Spheres Y-90 resin microspheres appear to have a favourable risk/benefit profile and offer clinicians a more targeted approach for the management of liver-dominant mCRC.\textsuperscript{12}
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