The FOXFIRE Combined Analysis

The 2004 introduction of FOLFOX, a chemotherapy regimen of fluorouracil (5-FU), leucovorin and oxaliplatin was a milestone in the evolution of first-line therapy of patients with unresectable metastatic colorectal cancer (mCRC): The use of FOLFOX and the development of combinations with other chemotherapeutic agents such as irinotecan, the emergence of biologically targeted agents such as bevacizumab and cetuximab, as well as the availability of genetic assays such as *RAS* gene mutation testing have enabled mCRC patients to survive more than twice as long as was possible at the turn of the 21st Century.

At the same time, mCRC is increasingly understood to be a heterogeneous disease with differing histological features, outcomes and clinical responses. Over the past decade, for example, researchers have found increasing evidence that primary tumour location within the colon is an important prognostic factor for both early and advanced colorectal cancer. Those mCRC patients who present with a right-sided primary tumour are clinically more difficult to treat, because they are less responsive to standard of care chemotherapies and have fewer treatment options available, since the tumours do not respond to some biologic agents such as EGFR inhibitors (cetuximab and panitumumab).[1]

Clinical research studying the addition of Selective Internal Radiation Therapy (SIRT) in the form of SIR-Spheres® Y-90 resin microspheres to first-line standard of care mCRC regimens aims to further improve the outcome for many of these patients.

The FOXFIRE Combined Analysis assesses the Overall Survival (OS) data from three randomised, controlled clinical studies called FOXFIRE, FOXFIRE Global and SIRFLOX. These three studies compared SIR-Spheres Y-90 resin microspheres in combination with standard-of-care chemotherapy to chemotherapy alone in first-line treatment of metastatic colorectal cancer (mCRC).

The combined OS analysis allowed pooling the data from 1,103 patients and provided sufficient statistical power to examine the survival benefit from the addition of SIR-Spheres Y-90 resin microspheres to current chemotherapy.[2]

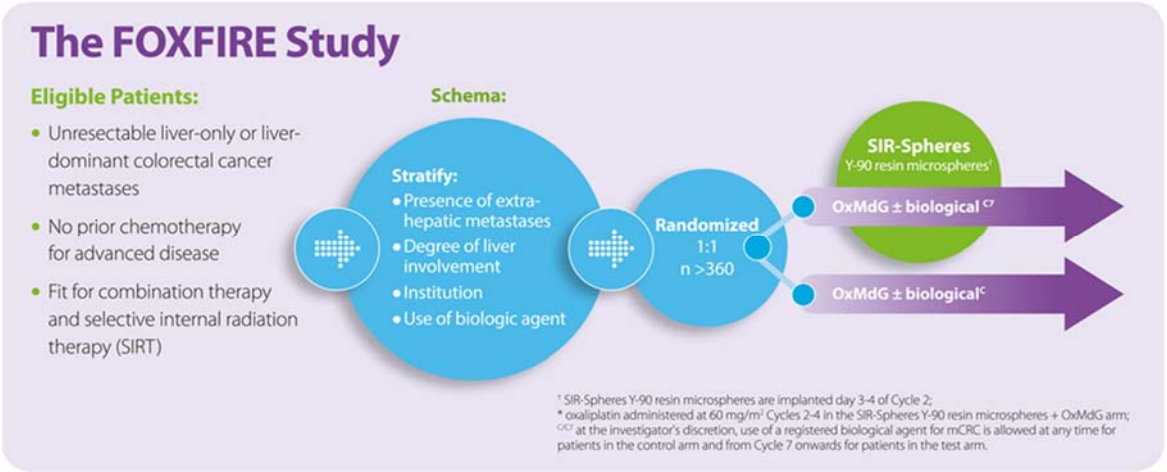
The data from the FOXFIRE-SIRFLOX combined OS analysis were presented at ASCO 2017.

What is the design of the FOXFIRE-SIRFLOX studies?

FOXFIRE and FOXFIRE Global were designed from the outset to allow for a combined analysis together with the clinical data from the SIRFLOX study. All three studies share a very similar design based on the chemotherapy regimen, mFOLFOX6, also known as modified de Gramont oxaliplatin regimen (OxMdG), with or without the addition of biologic agents.

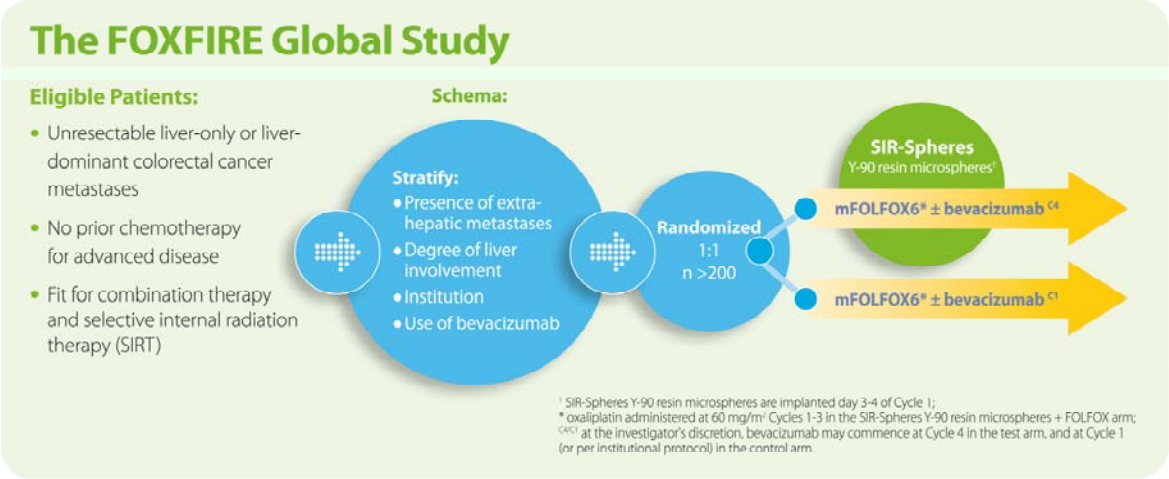
The **FOXFIRE study** enrolled more than 360 patients, with unresectable, liver-only or liver-predominant mCRC, in 32 UK cancer centres. The study was initiated in 2008 by the Oxford Oncology Clinical Trials Office (OCTO) in collaboration with the UK National Cancer Research Institute and completed patient enrolment in 2014.[3]

In FOXFIRE, the use of the biologic agents bevacizumab or cetuximab were allowed at the investigator's discretion and were stratified accordingly.

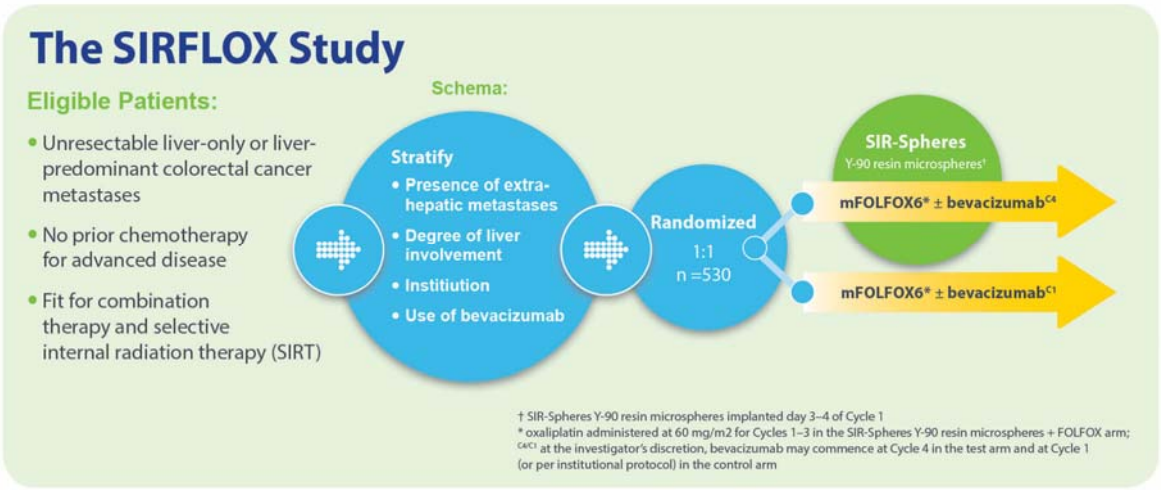


MEDIA BACKGROUNDER

The **FOXFIRE Global study** enrolled more than 200 patients. The study began in 2013 in a network of more than 80 centres in Australia, New Zealand, Asia Pacific, Israel, Western Europe and the United States. The study completed patient enrolment in 2014.



The **SIRFLOX study** was the first large-scale, randomised controlled trial (RCT) of 530 chemotherapy-naïve patients with liver-only or liver-dominant mCRC and examined whether the combination of SIR-Spheres Y-90 resin microspheres with first-line chemotherapy was more effective than chemotherapy alone. The SIRFLOX study results were published in JCO in early 2016.[2] The results showed that the addition of SIR-Spheres Y-90 resin microspheres significantly improved median Progression Free Survival (PFS) in the liver by 7.9 months, corresponding to a 31% reduction in risk of progression in the liver.[4]



What types of patients were included in the FOXFIRE-SIRFLOX studies?

The patient selection criteria of all three studies were similar. In FOXFIRE, there was no limitation in the size of lung or lymph node metastases, and no organ restriction of the extra hepatic metastases compared to FOXFIRE Global and SIRFLOX.

The following study inclusion criteria were used:

- Unresectable liver-only or liver-predominant tumours that have spread from the bowel;
- No prior chemotherapy for advanced disease;
- Fit for combination therapy and Selective Internal Radiation Therapy (SIRT).

What types of patients were excluded from the FOXFIRE-SIRFLOX studies?

Patients were excluded if, for example, they had liver disease such as cirrhosis; prior chemotherapy for advanced bowel cancer; other types of cancer; or prior radiotherapy to the upper abdomen. Patients were also excluded if they were pregnant or were breast feeding at the time of the study.

What are the outcomes and implications of the FOXFIRE-SIRFLOX studies?

The primary endpoint of the 1,103-patient SIRFLOX, FOXFIRE and FOXFIRE Global Combined Analysis was to determine if there was an OS benefit of adding targeted radiation to the liver, in the form of SIR-Spheres Y-90 resin microspheres, to a current standard-of-care systemic chemotherapy regimen compared to chemotherapy alone in patients with inoperable liver metastases from primary colorectal cancer, with or without evidence of limited metastases outside the liver.

The combined analysis did not reach its primary endpoint of an overall survival (OS) benefit between patients treated with SIRT plus first-line chemotherapy compared to patients treated with chemotherapy alone. However, the study has significantly enriched scientific understanding of the role of SIRT in the management of mCRC, particularly in the liver, which is the organ of greatest risk and the ultimate cause of death for the majority of these patients.

The patients in the FOXFIRE Combined Analysis had a median age of 63 years (range of 23–90 years). All had been diagnosed recently with unresectable mCRC, which had metastasized primarily but not only to the liver. In a large number of cases (55.0% *vs.* 50.2% in the SIRT and chemotherapy arms, respectively), the patients' primary colorectal tumour was still in place when they entered the study. While no significant difference was found in OS (Hazard Ratio [HR]:1.04; p=0.609) or PFS (HR: 0.90; p=0.108), there was a significantly higher tumour Objective Response Rate (p=0.001) and 49% better Progression Free Survival in the liver (HR: 0.51; p<0.001) among the patients treated with Y-90 resin microspheres.[5]

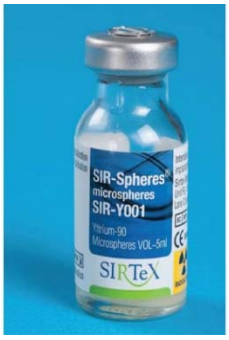
"In my experience, although overall survival is the gold standard endpoint for randomised phase III clinical trials, it is often difficult to see statistically significant results when patients like the ones we treated have received multiple lines of therapy after they receive the new treatment. There is also no way of controlling cross-over to a new treatment after the patient has completed protocol therapy, as was the case with the one-in-eight (12%) chemotherapy-only patients in these studies who went on to receive SIRT," Professor Sharma, the principle investigator of the FOXFIRE Combined Analysis, said.[6]

"Furthermore, even in a very large study like this one, it is difficult to control for all biological factors since researchers are still discovering previously unknown factors that drive cancer. Our findings in patients with right-sided primary tumours are an example of this. When we designed the SIRFLOX and FOXFIRE studies a decade ago, colorectal cancer was classified as a single disease; only recently has it been shown that right-sided colorectal cancer is, in fact, a different disease process genetically and a challenge to the physicians who treat it," said Prof. Sharma.[6]

Importantly, in subgroup analyses of the FOXFIRE studies, a strong signal was identified indicating that the addition of SIR-Spheres Y-90 resin microspheres to first-line chemotherapy for mCRC may significantly increase OS in patients with right-sided primary colon tumours, whose median overall survival increased by 4.9 months and risk of death was reduced by 36% (HR: 0.64; 95% CI: 0.46–0.89; p=0.007).[5,7]

The FOXFIRE investigators believe that this unanticipated finding may prove to be clinically meaningful, as patients with right-sided primary colon tumours represent more than a third (35–38%) of all metastatic colon cancer patients.[8] This group of patients have a very poor prognosis compared to patients with other colorectal cancers, represent a major unmet medical need with fewer treatment options available and are an important focus of cancer research today.

Detailed analysis of outcomes by primary tumour location in the SIRFLOX-FOXFIRE Global cohorts are expected to be presented at the ESMO World Congress of Gastrointestinal Cancer, 28 June – 1 July 2017.



SIR-Spheres Y-90 resin microspheres are tiny radioactive resin beads that emit beta radiation and possess unique physical characteristics and biological effects.[9] They are only about one third the width of a human hair and have about the same specific gravity as a red blood cell. This enables the microspheres to flow easily in the blood and become lodged in the small blood vessels around the liver tumour where they destroy it while sparing the surrounding healthy tissue.

For more information please visit:
www.sirtex.com

1. Clinical Practice Guidelines in Oncology (NCCN® Guidelines), Colon Cancer Version 2.2017 – March 13, 2017 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
2. Virdee PS *et al. JMIR Res Protoc* 2017, **28**; ePub doi: 10.2196/resprot.7201.
3. Dutton SJ *et al. BMC Cancer* 2014; **14**: 497.
4. van Hazel GA *et al. J Clin Oncol* 2016; **34**:1723–31.
5. Sharma RA *et al. 2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.
6. Sirtex Medical Ltd. Announcement. 5. June 2017.
7. Data on file.
8. Petrelli F *et al. JAMA Oncol* 2017; **3**: 211–19.
9. Walrand S *et al. J Nucl Med* 2014; **8**:1317–22.

MEDIA BACKGROUNDER