# FOXFIRE Combined Analysis Results in First-Line Treatment of Metastatic Colorectal Cancer Presented at ASCO

## Overall Survival (OS) findings reviewed in detail; Potential median OS benefit in mCRC patients with right-sided primary colon cancer

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Results of the FOXFIRE Combined Analysis, a study of 1,103 patients randomised to receive either standard first-line chemotherapy for colorectal cancer that has spread to the liver, or the same chemotherapy plus a treatment procedure called selective internal radiation therapy (SIRT) using SIR-Spheres® Y-90 resin microspheres, were presented at the American Society of Clinical Oncology meeting by the co-principal investigator of the study, Professor Ricky Sharma, Chair of Radiation Oncology at University College London (UK), and Scientific Group Leader at the UCL Cancer Institute.[1]

"The FOXFIRE Combined Analysis is the largest cancer study ever conducted to investigate the combination of chemotherapy with an interventional radiology procedure, such as SIRT," Professor Sharma said. "We combined data from the SIRFLOX study first presented in 2015 with data from two new studies – FOXFIRE and FOXFIRE-Global."

"Our analysis did not meet its primary endpoint of an overall survival (OS) benefit for patients treated with SIRT plus first-line chemotherapy compared to patients treated with chemotherapy alone. Nonetheless, I believe this study has significantly enriched scientific understanding of the role of SIRT in the management of metastatic colorectal cancer, particularly in the liver. Finding more effective treatments remains a critical issue for these patients," Prof Sharma stated.

The 1,103 patients in the FOXFIRE Combined Analysis had a median age of 63 years (with a range of 23–90). All had been diagnosed recently with unresectable mCRC, which had metastasized either to the liver alone, or to the liver and limited additional sites in the lungs or lymph nodes. Almost all patients (87.2% *vs*. 86.5% in the SIRT and chemotherapy arms, respectively) presented with metastases at the same time as their primary diagnosis of CRC. In a large number of cases (55% *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 Progression-Free Survival [PFS] (HR: 0.90; p=0.108), there was a significantly higher tumour Objective Response Rate (p=0.001) and 49% reduced cumulative risk of progression in the liver as first event (HR: 0.51; p<0.001) among the patients treated with Y-90 resin microspheres.

Moreover, in an exploratory subgroup analysis of the FOXFIRE studies, the SIRFLOX and FOXFIRE Global study investigators discovered a strong signal indicating that the addition of Y-90 resin microspheres to first-line chemotherapy for mCRC may significantly increase OS in patients with right-sided primary colon tumours, increasing the median overall survival by 4.9 months and reducing the risk of death in this group at any timepoint by 36% (HR: 0.64; with a 95% Confidence Interval from 0.46–0.89; p=0.007).

"Following further validation, this unexpected finding may prove to be clinically meaningful," Prof Sharma explained, "as patients with right-sided primary colon tumours represent more than a third (35–38%) of all colon cancer patients.[2] They have a very poor prognosis compared to patients with other colorectal cancers, which represents a major unmet medical need and an important focus of cancer research today."

Detailed analysis of 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.

"There is no question that Y-90 resin microspheres are highly active against liver metastases and are a mainstay of treatment of mCRC for patients who cannot tolerate or no longer respond to chemotherapy," Professor Sharma continued, "but we must also try to understand why our analysis fell short of its primary endpoint."

"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 said.

"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."

## About Colorectal Cancer

Colorectal cancer is the fourth most frequently diagnosed cancer worldwide, and the third leading cause of cancer deaths, taking almost 700,000 lives annually.[3] More than half of all patients with colorectal cancer will be diagnosed with metastases, most commonly in the liver.[4,5]

## About The FOXFIRE Combined Analyses

The FOXFIRE-SIRFLOX Combined Analysis assesses the Overall Survival (OS) and other outcomes 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 FOXFIRE study is an investigator-initiated study funded by the Bobby Moore Fund of Cancer Research UK, sponsored by the University of Oxford and supported by Sirtex Medical. The FOXFIRE Global and SIRFLOX studies were sponsored by Sirtex Medical.

**What is SIRT with SIR-Spheres Y-90 resin microspheres?**

SIRT with SIR-Spheres Y-90 resin microspheres is an approved treatment for inoperable liver tumours. It is a minimally-invasive treatment that delivers high doses of high-energy beta radiation directly to the tumours. SIRT is administered to patients by interventional radiologists, who infuse millions of radioactive resin microspheres (diameter between 20–60 microns) via a catheter into the liver arteries that supply blood to the tumours. By using the tumours' blood supply, the microspheres selectively target liver tumours with a dose of radiation that is up to 40 times higher than conventional radiotherapy, while sparing healthy tissue.

SIR-Spheres Y-90 resin microspheres are approved for use in Argentina, Australia, Brazil, the European Union (CE Mark), Switzerland, Turkey, and several countries in Asia for the treatment of unresectable liver tumours. In the US, SIR-Spheres Y-90 resin microspheres have a Pre-Market Approval (PMA) from the FDA and are indicated for the treatment of unresectable metastatic liver tumours from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (floxuridine).

**About Sirtex**

Sirtex Medical Limited (ASX: SRX) is an Australian-based global healthcare business working to improve treatment outcomes in people with cancer. Our current lead product is a targeted radiation therapy for liver cancer called SIR-Spheres Y-90 resin microspheres. Approximately 73,000 doses have been supplied to treat patients with liver cancer at more than 1060 medical centres in over 40 countries. For more information, please visit www.sirtex.com.



**References:**

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