



SIRFLOX Study Published in Journal of Clinical Oncology

Prestigious ASCO Journal Publishes 530-patient SIRFLOX Study on SIR-Spheres® Y-90 resin microspheres in the Management of Metastatic Colorectal Cancer (mCRC)

Sydney, Australia (23 February 2016) – Sirtex Medical Limited (ASX: SRX) announced that the results of the SIRFLOX study with SIR-Spheres Y-90 resin microspheres have been published on-line in the *Journal of Clinical Oncology* (JCO), the leading peer-reviewed publication of the American Society of Clinical Oncology (ASCO).¹ Initial study findings were reported in an oral abstract presentation at the ASCO Annual Congress in Chicago, USA, in May 2015.

JCO has published the SIRFLOX study as a “Rapid Communication”, which they define as a commitment to freely disseminate ground-breaking and practice-changing information so that it may benefit all readers and patients.

Lead author and the study’s co-principal investigator, Prof. Guy A van Hazel of the University of Western Australia, Perth, Australia, said “In the primary endpoint of the study, patients with non-resectable liver-dominant or liver-only colorectal cancer who received FOLFOX-based first-line chemotherapy alone had a median Progression-Free Survival (PFS) at any site of 10.2 versus 10.7 months in those that received chemotherapy plus SIR-Spheres, but this difference was not statistically significant. However, the addition of SIR-Spheres Y-90 resin microspheres to chemotherapy significantly prolonged PFS in the liver, from a median of 12.6 months in the chemotherapy control arm compared to 20.5 months in the SIR-Spheres arm, which translated to a 31 percent reduction in the risk of tumour progression in the liver. Long-term disease control is critical as liver metastases eventually cause the death of the majority of the hundreds of thousands of patients who get colorectal cancer that cannot be removed by surgery.”

Gilman Wong, CEO of Sirtex Medical Limited, said that, “Today’s publication of the SIRFLOX study results represents both a culmination and a beginning for our company. SIRFLOX has been for us a ten-year journey to demonstrate in the clearest scientific terms that SIR-Spheres Y-90 resin microspheres belong among the first-line options that oncologists can use to treat mCRC. The publication of SIRFLOX in JCO is definitive recognition of the relevance of our technology in the control of liver metastases from colorectal cancer.”

Mr Wong added that, “We remain hopeful that our pre-planned, combined analysis of the SIRFLOX data with the findings of the FOXFIRE and FOXFIRE Global studies, which will be available in 2017, will give us a clear indication of the survival benefit associated with adding SIR-Spheres Y-90 resin microspheres to a standard-of-care chemotherapy.”

SIRFLOX Findings

The SIRFLOX study recruited 530 patients who had been diagnosed with unresectable mCRC at 87 medical centres in Australia, Europe, Israel, New Zealand, and USA, between October 2006 and April 2013. Of these 530 patients, 263 control patients were randomized to be treated with the mFOLFOX6 regimen of 5FU, leucovorin and oxaliplatin, with the biological agent bevacizumab allowed at local investigator’s discretion. The other 267 patients received selective internal radiation therapy (SIRT)

with SIR-Spheres Y-90 resin microspheres in addition to the mFOLFOX6 chemotherapy regimen (\pm bevacizumab).

The primary endpoint of SIRFLOX was Progression Free Survival (PFS) at any site. Patients in the SIRFLOX control arm had a PFS at any site of 10.2 versus 10.7 months in the SIRT arm, but this difference was not statistically significant, with a hazard ratio (HR) of 0.93 and $P = 0.43$.

However, in respect to the study's key secondary endpoint of median PFS in the liver, which is the organ that SIR-Spheres Y-90 resin microspheres directly targets, the difference was 12.6 versus 20.5 months in control versus SIRT by competing risk analysis. The Hazard Ratio (HR) was 0.69 ($P = 0.002$), representing a 31% gain with the addition of SIRT. In addition, while objective treatment response rate (ORR) at any site was similar (68.1% versus 76.4% in control versus SIRT; $P = 0.113$), ORR in the liver was improved with the addition of SIRT (68.8% versus 78.7% in control versus SIRT; $P = 0.042$), with complete responses in the liver increased over three-fold (1.9% versus 6.0% in control versus SIRT; $P = 0.020$).

Grade ≥ 3 adverse events (AEs) were reported in 73.4% and 85.4% patients in control versus SIRT ($P = 0.516$), including recognized SIRT-related effects. The safety profile of the combined therapy was noted by the investigators as being as expected and consistent with previous studies.

Prof. van Hazel and his co-authors concluded that, "The median 20.5 month liver PFS for patients treated with chemotherapy plus SIRT represents a substantial prolongation of local disease control compared to systemic chemotherapy alone, which was a median 12.6 months."

They go on to explain that as SIRFLOX was the first study ever to evaluate PFS in the liver, there are no other studies that provide context to this finding. They point out, however, that "recently reported data from the CLOCC study, which combined radiofrequency ablation (RFA) with FOLFOX-based systemic chemotherapy in patients with unresectable mCRC confined to the liver, demonstrated that improved control of hepatic metastases can translate to a substantial impact on overall survival."

Prof. van Hazel and his colleagues note that overall survival is a secondary outcome for the SIRFLOX study, and that, "During the 7-year recruitment period of the study, when it became evident that improved patient care and new chemotherapy regimens were extending survival for mCRC patients receiving first-line chemotherapy treatment, a decision was made to pre-plan a combined survival analysis including data from SIRFLOX and two additional randomized studies, FOXFIRE and FOXFIRE Global."

"In all three studies," they state, "SIRT has been added to oxaliplatin-based chemotherapy in an almost identical patient population. The FOXFIRE and FOXFIRE Global studies have completed accrual and combined with SIRFLOX have a total recruitment of over 1,100 patients; this provides adequate power to detect a survival advantage," with findings expected to be reported in 2017.

About SIR-Spheres Y-90 resin microspheres

SIR-Spheres Y-90 resin microspheres are a medical device used in an interventional radiology procedure known as selective internal radiation (SIRT), or radioembolisation, which targets high doses of radiation directly to liver tumours. The treatment consists of tens of millions of radioactive Y-90 coated resin particles, each no bigger in diameter than a human hair. Interventional radiologists inject these resin particles, or microspheres, into the hepatic artery via a catheter inserted into the femoral artery through an incision in the groin. The SIR-Spheres Y-90 resin microspheres become lodged in the capillaries that surround liver tumours, where they deliver a high dose of short-range (mean 2.5 mm; maximum 11 mm) beta radiation to the liver tumours, while sparing healthy liver

tissue. The low specific gravity of Y-90 resin microspheres allows the blood flow to evenly distribute the radioactivity within and around the liver tumours.

SIR-Spheres Y-90 resin microspheres are approved for the treatment of inoperable liver tumours in Australia, the European Union (CE Mark), Argentina (ANMAT), Brazil and several countries in Asia such as India, Singapore and Turkey. The product is also supplied for this use in countries such as Hong Kong, Israel, Malaysia, New Zealand, Taiwan and Thailand. SIR-Spheres Y-90 resin microspheres are approved in the United States (FDA PMA approval) for the treatment of non-resectable metastatic liver tumours from primary colorectal cancer in combination with intra-hepatic artery chemotherapy using 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 55,000 doses have been supplied to treat patients with liver cancer at more than 900 medical centres in over 40 countries. For more information, please visit www.sirtex.com.

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Reference:

1. van Hazel GA, Heinemann V, Sharma NK *et al* on behalf of the SIRFLOX Study Group. SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. *Journal of Clinical Oncology* 2016 February 22; ePub doi: 10.1200/JCO.2015.66.1181.

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