SIRTEX CLINICAL STUDY PROGRAM

Sirtex’s extensive clinical study program means that SIR-Spheres® Y-90 resin microspheres are by far the most-studied SIRT (Selective Internal Radiation Therapy) technology for treating liver tumors.

The clinical study program has been designed to:

- Define the optimal role for SIR-Spheres® Y-90 resin microspheres in the treatment of various inoperable liver tumors.
- Further investigate the safety and effectiveness of SIR-Spheres® Y-90 resin microspheres with chemotherapy and biologic agents.
- Expand the indications for SIR-Spheres® Y-90 resin microspheres including its application to other cancers.
- Improve the administration of SIR-Spheres® Y-90 resin microspheres.

Clinical study programme in numbers

- 21 studies in progress.
- 26 countries are participating.
- More than 2,000 patients enrolled.
- Collaborating with more than 100 academic and scientific institutions and 1,000 researchers.

Investigating the earlier use of SIR-Spheres® Y-90 resin microspheres in liver tumors

Sirtex is supporting an extensive clinical study program of randomised controlled studies. They are the largest studies of their kind in the world and are designed to demonstrate the efficacy of SIR-Spheres® Y-90 resin microspheres as a first-line treatment for liver cancer.

1 Primary liver cancer (cancer originating in the liver)

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC, or bile duct cancer) are the two leading forms of primary liver cancers.1,2

The SARAH and SIRveNIB studies are two large multi-centre randomised controlled studies that compare the efficacy and safety of SIR-Spheres® Y-90 resin microspheres with Sorafenib – the current standard of care for unresectable locally advanced hepatocellular carcinoma. The SARAH trial in Europe completed enrolment in March 2015 with more than 400 patients from 25 centres throughout France. The study results will be presented at the European Association for the Study of the Liver (EASL) congress in April 2017.

The SIRveNIB trial in Asia completed its planned enrolment of 360 patients in May 2016. The findings of the SIRveNIB study comparing SIR-Spheres® Y-90 resin microspheres with Sorafenib are expected to be presented at medical congresses in 2017.

VESPRO, a prospective meta-analysis will combine the impending results of these two large randomised studies. Results from the VESPRO meta-analysis are also expected to be available in 2017.

In addition to these two “head-to-head” studies, a third large European randomised controlled study called SORAMIC is comparing treatment of HCC with SIR-Spheres® Y-90 resin microspheres followed by Sorafenib to the treatment with Sorafenib alone. Results from SORAMIC are expected to be available in 2018.

The SIRCCA study is a large multi-centre randomised controlled study that will evaluate the benefit of applying SIR-Spheres® Y-90 resin microspheres prior to receiving systemic chemotherapy treatment (cisplatin-gemcitabine, or CIS-GEM) in patients with unresectable intrahepatic cholangiocarcinoma (ICC). The primary outcome of the SIRCCA study is survival at 18 months after randomization.

2 Metastatic Colorectal Cancer (cancer that has spread to the liver)

Secondary liver cancer is more common than primary liver cancer.3 Any cancer has the potential to spread to the liver with the most common being colon, breast and lung cancers.4

Sirtex has a mature and extensive clinical research program investigating the first-line use of SIR-Spheres® Y-90 resin microspheres in combination with a current standard-of-care chemotherapy in patients with recently diagnosed non-resectable colorectal cancer tumors that have spread to the liver.
Three large, randomised controlled clinical studies – SIRFLOX, FOXFIRE and FOXFIRE Global – will report their results in a combined overall survival (OS) analysis.\textsuperscript{5} The FOXFIRE-SIRFLOX combined OS analysis allows pooling of data from 1,103 patients and will provide sufficient statistical power to examine the survival benefit from the addition of SIR-Spheres® Y-90 resin microspheres to current chemotherapy. The data from the FOXFIRE-SIRFLOX combined OS analysis are expected to be available in 2017.

FOXFIRE and FOXFIRE Global share a similar protocol and were designed from the outset to allow for a combined analysis together with the clinical data from the SIRFLOX study.

The FOXFIRE study enrolled more than 360 patients with unresectable liver-only or liver-dominant mCRC in 32 UK cancer centers. The study was initiated in 2008 by the University of Oxford’s Oncology Clinical Trials Office (OCTO) in collaboration with the UK National Cancer Research Institute. Patient enrolment was completed in 2014.

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

SIRFLOX is a prospective, open-label, multi-center, randomised controlled study. SIRFLOX enrolled 530 patients and is the world’s largest randomised interventional radiology study in oncology.\textsuperscript{6} The study was conducted at centers in Australia & New Zealand, Europe, the Middle East and North America.

The findings of the SIRFLOX study were reported at the American Society of Clinical Oncology (ASCO) 2015 Annual Meeting and published on-line as a Rapid Communication in February 2016 in the \textit{Journal of Clinical Oncology}.\textsuperscript{6}

The study results demonstrated that the addition of SIR-Spheres® Y-90 resin microspheres to standard chemotherapy in patients with liver-dominant mCRC did not improve PFS at any site but significantly prolonged PFS in the liver by 7.9 months (20.5 vs 12.6 months; \( p = 0.002 \)). This resulted in a 31% reduction in the risk of progression in the liver, which is the organ in which the radiotherapy targets tumors.\textsuperscript{6}

Investigating treatment of other liver tumors

Several studies are being conducted investigating the effect of SIR-Spheres® Y-90 resin microspheres in tumors that have spread to the liver from such areas as ocular melanoma (eye cancer) and breast cancer.

Expanding use beyond the liver

Sirtex is broadening its focus to examine the use of SIR-Spheres® Y-90 resin microspheres in a number of other cancers. Leading this program is the RESIRT study, which looks at the treatment of primary kidney cancer. The initial safety and efficacy results of RESIRT were presented at the European Society for Medical Oncology (ESMO) Congress in Copenhagen in October 2016.\textsuperscript{7}

Planning is also underway to investigate the treatment of SIR-Spheres Y-90 resin microspheres for the treatment of cancers in other organs.

In the United States SIR-Spheres® Y-90 resin microspheres are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy using floxuridine.

For more information please visit:

www.sirtex.com

\textsuperscript{1} EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012; 56: 908–43
\textsuperscript{3} Ananthakrishnan A et al. Semin Intervent Radiol 2006; 23: 47–62.
\textsuperscript{5} Virdee PS et al JMIR Res Protoc 2017, 28; ePub doi: 10.2196/resprot.7201.
\textsuperscript{7} de Souza P et al. ESMO Annual Meeting, Ann Oncol 2016; 27 (Suppl 6): Abs 803P.