Patients with Colorectal Cancer Liver Metastases Had Significantly Greater Depth of Tumour Response to SIR-Spheres® Y-90 resin microspheres, New SIRFLOX Analysis Shows

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New data presented by Prof. Dr. Volker Heinemann in an oral abstract session at the European Society of Medical Oncology's 18th World Congress on Gastrointestinal Cancer suggest that patients with liver-dominant mCRC treated first-line with the combination of mFOLFOX6 and SIR-Spheres Y-90 resin microspheres in the recently published SIRFLOX study experienced a much more profound response to treatment in the liver than those who received chemotherapy alone.[1]

According to Depth of Response (DpR) analysis, a relatively new methodology that has been shown to correlate with overall survival (OS) and post-progression survival in earlier mCRC studies,[2] there was a significantly greater Depth of Response (75.0% *vs*. 67.8% mean reduction in liver tumour burden; p=0.039) in patients who received SIR-Spheres Y-90 resin microspheres combined with chemotherapy. Patients also had a statistically significant, two-month longer time to DpR or maximal tumour shrinkage (median 266 *vs*. 206 days; p<0.001), compared to those who received chemotherapy alone.

The analysis also revealed that the treatment effect following SIR-Spheres Y-90 resin microspheres was most evident in the patients who entered the study with a greater baseline liver tumour burden (>12% of the liver having been replaced by tumour, a statistical cut-point that was pre-determined in order to identify potential predictors of DpR). This group of more compromised patients, representing over half the patients in SIRFLOX, experienced a statistically significant, 20% greater DpR (77.5% *vs*. 57.2%; p=0.003) and over three-month longer time to DpR (median 298 *vs*. 196 days; p<0.001) compared to those treated with chemotherapy alone. SIR-Spheres Y-90 resin microspheres was also associated with a doubling of median Progression-Free Survival (PFS) in the liver by competing risk analysis (27.2 *vs*. 13.1 months; p=0.003) in these patients.

Conversely, patients who had a smaller liver tumour burden (≤12%) on study entry were more than six times more likely to experience a complete response or disappearance of all liver tumours following SIR-Spheres Y-90 resin microspheres compared to those who received only chemotherapy (11.3% *vs.* 1.7%; p=0.003).

Prof. Heinemann, Professor of Medical Oncology at the Comprehensive Cancer Centre, Ludwig-Maximillian University, Munich, Germany, and European Principal Investigator of the SIRFLOX study stated that, "As treatment for metastatic colorectal cancer has improved over the past two decades, life expectancies have increased four-fold. But this increased survival benefit in turn has raised the barrier of proof of efficacy for new therapies or combinations of therapy that have emerged."

"Oncologists have for some time observed that Progression-Free Survival, or PFS, is not always a good predictor of overall survival for patients with metastatic colorectal cancer, as has been seen in some studies with biologic agents," Prof. Heinemann explained. "For this reason, in recent years we have seen an important surge of activity to find better surrogate markers for overall survival in mCRC, particularly regarding the effect of treatment on patients' Depth of Response. The greater depth of response and time to maximal response following SIR-Spheres Y-90 resin microspheres, together with the prolonged PFS in the liver, are very encouraging and increase our anticipation for the survival data we hope to see in 2017."

The DpR concept and methodology were developed by Prof. Heinemann and his colleagues in Munich, in collaboration with other experts in treating colorectal cancer. In the SIRFLOX DpR analysis, a novel volumetric model was used to estimate each patient's spherical liver tumour volume, based on the length of up to five target liver tumours, which were selected during a central independent blinded imaging review of the patients' baseline and subsequent radiographic images. DpR was then measured by tracking tumour shrinkage until it reached its lowest point, or nadir. In previous DpR analyses of the FIRE-3 study with the biologic agent cetuximab, Prof. Heinemann observed a statistically significant correlation between DpR and overall survival.[2] This observation has also been supported by an evaluation of the TRIBE study.[3]

"We were able to complete this DpR analysis because the original SIRFLOX methodology included extensive radiographic data to determine response to treatment using traditional RECIST criteria. But that is the beauty of this methodology; when the right dataset is available we don't need any new information to estimate the volumes and shed potentially important new light on the original findings," Prof. Heinemann added.

The predictive value of this approach may be corroborated when overall survival data on the combined SIRFLOX, FOXFIRE and FOXFIRE Global studies of the association of mFOLFOX6 and SIR-Spheres Y-90 resin microspheres in the first-line treatment of colorectal cancer liver metastases become available in 2017.

About SIRFLOX

The SIRFLOX study is the world's largest randomised interventional radiology study in oncology with 530-patients enrolled.[4] SIRFLOX investigated 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 tumours in the liver that have spread from the bowel. The study was a prospective, open-label, multi-centre, randomised controlled study, being conducted at sites in Australia & New Zealand, Europe, the Middle East and North America.

The primary endpoint of SIRFLOX was progression-free survival (PFS) at any site, as determined by independent central imaging review of CT or MRI scans. PFS involves finding out how long a person survives without the cancer developing any further. In patients with secondary tumours from bowel cancer, improved PFS typically correlates with improved overall survival.[5-7] PFS in the liver was also an important secondary endpoint of SIRFLOX, and other endpoints were tumour response rate in the liver; tumour response rate at any site; liver resection rate; hepatic and extrahepatic recurrence rate; health-related quality of life; toxicity and safety and overall survival.

The patients recruited in the SIRFLOX study had unresectable colorectal cancer liver metastases, with approximately 40% also having metastatic spread to the lungs and/or lymph nodes, and 45% had intact primary colorectal tumours. About 90% of the patients had synchronous disease, meaning that the distant spread of the cancer was confirmed around the same time as the primary tumour was diagnosed. Patients with synchronous disease have a worse prognosis compared to those who develop spread to distant sites sometime after the primary tumour is diagnosed and surgically removed.[8]

The SIRFLOX study results show no significant difference in Progression-Free Survival (PFS) at any site in the patients who received chemo-radiotherapy. This was not surprising as SIR-Spheres Y-90 resin microspheres are a liver-directed therapy and do not have an effect on metastases outside the liver. However, the investigators reported a significantly prolonged PFS in the liver by competing risk analysis – from a median of 12.6 months for control patients to 20.5 months (p=0.002) for patients receiving SIR-Spheres Y-90 resin microspheres – resulting in a 31% reduction in the risk of progression in the liver, which is the organ in which the radiotherapy targets tumours.

Overall survival will be reported subsequently as part of a combined survival analysis including data from two additional randomised controlled studies. These studies, which share a very similar design to SIRFLOX, are called FOXFIRE, which is being conducted in the UK, and an international study called FOXFIRE Global. Together, these additional studies have completed enrolment of 573 patients, in addition to those in SIRFLOX. Pooling the data from more than 1,100 patients will provide sufficient statistical power to examine the survival benefit from the addition of SIR-Spheres Y-90 resin microspheres to current chemotherapy. The survival data from the three combined studies are expected to be released in 2017.

About SIR-Spheres Y-90 resin microspheres

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, SIR-Spheres Y-90 resin microspheres, is a targeted radiation therapy for liver cancer. Approximately 61,000 doses have been supplied to treat patients with liver cancer at more than 1000 medical centres in over 40 countries. For more information, please visit www.sirtex.com.

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