New Analysis Reveals First-Line Treatment Data on SIR-Spheres® Y-90 resin microspheres for Patients with Liver Metastases from Right-Sided Primary Colon Cancer

SIRFLOX and FOXFIRE Global findings suggest that adding liver-directed Selective Internal Radiation Therapy (SIRT) to standard first-line chemotherapy may improve overall survival in metastatic colorectal cancer (mCRC) patients with right-sided primary tumours, compared to those receiving chemotherapy alone

Barcelona, Spain (3 July 2017) –

A *post-hoc* analysis of data from the 739-patient SIRFLOX and FOXFIRE Global studies indicates that adding SIRT with liver-directed SIR-Spheres® Y-90 resin microspheres to standard first-line mFOLFOX6 chemotherapy for liver-only or liver-dominant metastatic colorectal cancer (mCRC) in patients with right-sided primary (RSP) tumours led to a statistically significant and clinically meaningful 4.9-month median overall survival benefit (Hazard Ratio [HR]: 0.64 [95% CI: 0.46–0.89]; p=0.007). This translates into a 36% reduction in the risk of death at any given time compared to patients who received chemotherapy alone.[1]

"This striking and essentially unexpected finding may bring new hope to mCRC patients with liver-only or liver-dominant tumours that have spread from the right side of the bowel or colon. These cancers are genetically and structurally different from tumours that start on the left side of the colon. Patients with RSP tumours have a worse prognosis for survival and fewer treatment options. They do not respond well to biological therapies such as cetuximab or panitumumab," said Prof. Guy van Hazel, Clinical Professor of Medicine at the University of Western Australia, Perth, who presented the new data at the European Society of Medical Oncology's 19th World Congress on Gastrointestinal Cancer (WCGC) in Barcelona.[1]

The new data are consistent with a 2016 meta-analysis of 66 studies involving more than 1.4 million CRC patients, which found a significant prognostic impact of primary tumour site on overall survival.[2] In particular, patients with mCRC from a left-sided primary (LSP) tumour had a 27% reduced risk of death at any given time compared to RSP patients (HR: 0.73; p<0.001).[2] Patients with RSP represented more than a third (35–38%) of mCRC cases in this analysis.[2]

"We had not defined primary tumour 'sidedness' as a formal endpoint in the SIRFLOX and FOXFIRE Global studies, which we originally designed in 2005. At that time, scientific understanding of tumour site as a potentially significant variable in the management of CRC was only beginning to emerge," Prof. van Hazel explained. "However, we had a strong academic interest in the subject and were prescient

enough to record primary tumour location for every patient we enrolled and to look at these data as an independent secondary variable in our statistical plan."

"We were not alone in our initial conservatism about the effect of tumour site in colorectal cancer," he noted. "It was only at the 2016 ASCO Annual Meeting, for example, that Prof. Alan Venook of the University of California, San Francisco, stated that, although earlier studies had introduced the idea that tumour location could affect colorectal cancer treatment outcomes, '*the effect we observed in our retrospective analysis of the Phase III CALGB/SWOG 80405 clinical trial appears to be far greater than we expected*,' and could change the course of disease management," Prof. van Hazel added.[3,4]

"Scientific debate must and will continue on this subject," he said, "but if primary tumour sidedness effectively splits colorectal cancer and its metastases into two very different diseases, then treatment paradigms must be carefully reassessed to assure the best possible treatment outcomes for each patient. Our findings do require further validation and, subject to this, may support considering earlier use of SIRT for mCRC patients with liver-only or liver-dominant metastases from right-sided primary tumours."

"It is also important to remember," Prof. van Hazel stated, "that the data we are reporting now are from first-line studies that combined SIRT with chemotherapy for patients with mCRC, and this does not alter previously established evidence supporting the role of SIRT using SIR-Spheres Y-90 resin microspheres in treating mCRC patients who have failed or are intolerant to initial chemotherapy that led to the recommendations in the ESMO and NCCN clinical guidelines."[5,6]

Detailed Findings of the Sidedness Analysis

The analysis of outcomes by primary tumour location that Prof. van Hazel presented at WCGC was based on new data from SIRFLOX, a 530-patient study first reported at ASCO in 2015 and published subsequently in the *Journal of Clinical Oncology*,[7] and FOXFIRE Global, a 209-patient study whose findings were first reported at the 2017 ASCO meeting along with the findings of FOXFIRE, a 364-patient UK study.[8]

The data from these three studies were pooled prospectively in the 1,103-patient FOXFIRE Combined Analysis, which was presented at ASCO in June 2017 by Prof. Ricky Sharma, Chair of Radiation Oncology at University College London, UK. This analysis showed no difference in the primary endpoint of overall survival from adding SIRT to first-line FOLFOX-based chemotherapy in liver-only or liver-dominant mCRC independent of the site of the patient's primary CRC tumour.[8] However, Prof. Sharma's ASCO presentation did call attention to the finding of a survival benefit for RSP patients treated with SIRT using SIR-Spheres Y-90 resin microspheres, and noted that further data would be provided.

Of the 739 patients recruited in the SIRFLOX and FOXFIRE Global studies and reported by Prof van Hazel at WCGC, 179 (24.2%) had an RSP tumour and 540 (73.1%) had an LSP tumour; 16 (2.2%) patients had a primary in both sides and the primary tumour location was unknown in 4 patients (0.5%).[1] As expected, patients with a RSP were older (mean: 64.4 *vs.* 61.6 years) and a higher proportion were female (42.5% *vs.* 32.0%), compared to those with a LSP, however there were no significant differences between the treatment arms by primary tumour location. Overall Survival was significantly improved by the addition of SIRT with SIR-Spheres Y-90 resin microspheres to first-line mFOLFOX6 chemotherapy (± bevacizumab) in mCRC patients with a right-sided primary tumour (median 22.0 *vs*. 17.1 months, with or without SIRT, respectively; HR: 0.64 [95% CI: 0.46–0.89]; p=0.007). No improvement in survival was seen from the

addition of SIRT to first-line mFOLFOX6 chemotherapy for patients with LSP tumours (median 24.6 *vs*. 26.6 months, with or without SIRT, respectively; HR: 1.12 [95% CI: 0.92–1.36]; p=0.279).

A standard statistical test of treatment interaction by location for overall survival also proved highly significant (Chi-square: 9.49; p=0.002; HR: 0.548 [95% CI: 0.37–0.80]), providing further evidence that the observed benefit of adding SIRT to mFOLFOX6 chemotherapy in RSP mCRC patients was not a chance finding.

Patients with RSP tumours treated with SIRT plus mFOLFOX6 also showed a trend towards improved Progression-Free Survival (PFS) compared with those who received mFOLFOX6 alone (median 10.8 *vs*. 8.7 months, respectively; HR: 0.73 [95% CI: 0.53–1.01]; p=0.053).

There were no significant differences in the incidence of adverse events (AEs) between patients with RSP tumours and those with LSP tumours. "Although AEs were more common in the chemotherapy plus SIRT group of the Combined Analysis, these were generally predictable and manageable," noted Prof. van Hazel.

Prof. van Hazel concluded that, "The location of the primary tumour in mCRC is emerging as a major prognostic factor and predictor of response to treatment. Patients with mCRC from right-sided primary tumours clearly have a worse prognosis and an inferior response to treatment compared to patients with left-sided primaries. Our analysis of the impact of primary tumour location on outcomes in the SIRFLOX and FOXFIRE Global studies cohorts shows that the addition of SIR-Spheres Y-90 resin microspheres to first-line FOLFOX-based chemotherapy was associated with a statistically significant and clinically relevant gain in Overall Survival for patients with a right-sided primary tumour."

"We believe that our data add to the growing literature on the impact of primary tumour location on mCRC outcomes, which has been observed with various treatments and may, if validated, support a side-based approach to patient selection for SIRT in first-line treatment of liver-only or liver-dominant mCRC."

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.[9] More than half of all patients with colorectal cancer will be diagnosed with metastases, most commonly in the liver.[10,11]

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.

SIR-Spheres® is a Registered Trademark of Sirtex SIR-Spheres Pty Ltd.

For further Information, contact:

Bianca Lippert, PhD, Sirtex Medical: blippert@sirtex.com +49 175 9458089
Ken Rabin, PhD, Sirtex Medical: krabin@sirtex.com +48 50227 9244

References:

1. van Hazel G, Heinemann V, Sharma N *et al.* Impact of primary tumour location on survival in patients with metastatic colorectal cancer receiving selective internal radiation therapy and chemotherapy as first-line therapy. *ESMO 19th World Congress on Gastrointestinal Cancer, Ann Oncol* 2017; Abs. LBA-006.
2. Petrelli F, Tomasello G, Borgonovo K *et al.* Prognostic survival associated with left-sided vs right-sided colon cancer: A systematic review and meta-analysis. *JAMA Oncol* 2017; **3**: 211–9.
3. Venook AP, Niedzwiecki D, Innocenti F *et al*. Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *2016 ASCO Annual Meeting; J Clin Oncol* 2016; **34** (Suppl): Abs 3504.
4. Medscape. Big Difference in Colorectal Cancer on Right vs Left Side. 2016 May 19; http://www.medscape.com/viewarticle/863537. Last accessed June 2017.
5. Van Cutsem E, Cervantes A, Adam R*, et al.* ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; **27**: 1386–1422.
6. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Colon Cancer. Version 2.2017 www.nccn.org/professionals/physician_gls/PDF/colon.pdf. Last accessed June 2017.
7. van Hazel GA, Heinemann V, Sharma NK *et al*. 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. *J Clin Oncol* 2016; **34**: 1723–1731.
8. Sharma RA, Wasan H, van Hazel G *et al*. Overall survival analysis of the FOXFIRE prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer. *2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.
9. GLOBOCAN 2012. Estimated cancer mortality, incidence and prevalence worldwide, Available at http://globocan.iarc.fr/Default.aspx. Last accessed June 2017.
10. Adam R, De Gramont A, Figueras J *et al.* The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 2012; **17**: 1225–39.
11. Van de Eynde M, Hendlisz A. Treatment of colorectal liver metastases: A review. *Rev Rec Clin Trials* 2009; **4**: 56–62.

783-EUA-0617