SIR-Spheres® Y-90 resin microspheres Substantially Improves Quality of Survival in Primary Liver Cancer, New Study against Standard Treatment Shows

459-patient SARAH Study shows that local treatments of advanced or inoperable Hepatocellular Cancer (HCC) with SIR-Spheres Y-90 resin microspheres did not lead to a planned superiority difference in overall survival compared to daily standard-of-care systemic therapy with sorafenib, yet had significantly reduced side effects and better Quality of Life

Amsterdam, 24 April 2017 -- Patients with advanced or inoperable Hepatocellular Carcinoma (HCC) who usually received one or two treatments with liver-directed SIR-Spheres Y-90 resin microspheres in the 459-patient French SARAH study had similar survival compared to patients who received standard twice-daily systemic treatment with sorafenib, but with less than half the number and significantly fewer severe treatment-related adverse effects and significantly better Quality of Life, according to data presented here at The International Liver Congress™ 2017.[1]

The results, which could impact the treatment of tens of thousands of liver cancer patients annually, were announced by the principal investigator of the SARAH study, Professor Valérie Vilgrain MD, PhD, Department of Radiology, Beaujon Hospital, Assistance Publique – Hôpitaux de Paris (AP-HP) and Université Paris Diderot, Sorbonne Paris Cité, France.

“Neither sorafenib nor SIR-Spheres Y-90 resin microspheres produced a statistically significant difference in Overall Survival (OS) of the patients we studied,” said Prof. Vilgrain. “Despite 26.6% of patients in the SIRT arm not receiving SIR-Spheres per protocol, the primary endpoint of Overall Survival by intention-to-treat [ITT] was not significantly different (median 8.0 *vs*. 9.9 months; p=0.18). Moreover, if we look at the patients who received SIR-Spheres or sorafenib according to the SARAH protocol, median OS was identical (9.9 *vs*. 9.9 months; p=0.92).”

“In terms of what matters for patients, the findings from this first large head-to-head comparison of liver-directed Selective Internal Radiation Therapy (SIRT) and systemic chemotherapy with sorafenib also show clearly that liver-directed procedures with SIR-Spheres result in a significantly better tolerance of treatment and quality of life,” Prof. Vilgrain stated. “I believe this consideration should be a critical factor in selecting first-line treatment for this patient population in the future.”

The difference in the frequency and severity of side effects of patients treated with SIR-Spheres Y-90 resin microspheres versus sorafenib was striking. Significantly fewer patients treated with SIR-Spheres Y-90 resin microspheres had any treatment-related side effects at all (76.5% *vs*. 94.0% for sorafenib; p<0.001), and these were also less severe (≥ grade 3; 40.7% *vs*. 63.0%, respectively; p<0.001). Moreover, those patients treated with SIR-Spheres Y-90 resin microspheres who reported treatment-related side effects experienced a median of only 5 such events over the course of the SARAH study, compared to a median of 10 events in those who received sorafenib (p<0.001).

General treatment-related symptoms such as fatigue (42% *vs*. 65%; p<0.001), abdominal pain (20% *vs*. 29%; p=0.032), nausea or vomiting (12% *vs*. 23%; p=0.001) and infection (4% *vs*. 11%; p=0.007) were also significantly less frequently reported and less severe for patients receiving SIR-Spheres Y-90 resin microspheres, compared to sorafenib.

Fewer patients receiving SIR-Spheres Y-90 resin microspheres experienced treatment-related diarrhoea (13% *vs*. 68% for sorafenib; p<0.001), hand-foot skin reaction (0.4% *vs.* 21%; p<0.001), anorexia (13% *vs.* 32%; p<0.001), weight loss (6% *vs.* 21%; p<0.001) and alopecia (0% *vs.* 16%; p<0.001), as well as infections (4% *vs.* 11%; p=0.007), hypertension (3% *vs.* 13%; p<0.001) and non-gastrointestinal haemorrhage (3% *vs.* 10%; p=0.002).

There were few potential SIRT-associated treatment-related complications and, importantly, no radioembolization-induced liver disease (radiation hepatitis) experienced. There were no significant increases for SIR-Spheres Y-90 resin microspheres in gastrointestinal (GI) ulceration (2% *vs.* 0.5% for sorafenib; p=0.37) including one case of radiation-induced GI ulcer, ascites (12% *vs.* 11%; p=0.57), hyperbilirubinemia (12% *vs.* 13%; p=0.86) and only one case of radiation pneumonitis (0.4% *vs.* 0; p=0.46).

The results of Quality of Life (QoL) surveys filled out by SARAH participants at three month intervals after their initial treatment underscored the benefit of SIR-Spheres Y-90 resin microspheres. "Based on their responses to the Global Health Status questions in the European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 questionnaire, patients treated with SIR-Spheres maintained their health status over the duration of the SARAH study, whereas patients receiving sorafenib reported a significant and sustained decline in QoL (group effect: p=0.005; time effect: p<0.001; between group difference increase over time: p=0.045)," Prof. Vilgrain said.

"In addition," she noted, "we found that the tumours of patients treated with SIR-Spheres had a higher objective response (19.0% *vs*. 11.6%; p=0.042) than was seen with sorafenib, and experienced a significantly reduced risk of their cancer progressing in the liver, which is the main cause of death from this disease."

Background of the SARAH Study

"Patients with HCC who are not eligible for liver transplant, surgery or ablation to treat their tumours in place face a very bleak prognosis of one or two years of life with increasing debilitation and pain," Prof. Vilgrain said. "In many cases, the patient's HCC is already so advanced that the main treatment option available is sorafenib. In other cases, we are able to treat patients with intermediate-stage disease initially with several courses of chemotherapy infused directly into their livers, which is called transarterial chemoembolisation, or TACE, but this approach may fail."

"For patients with advanced HCC or those failing TACE, we have for the past ten years relied upon oral systemic treatment with sorafenib, which was shown to extend survival compared to placebo, but also causes many side effects that can compromise patients' quality of life. That is why we

decided to see if treatment with a newer form of liver-directed therapy, selective internal radiotherapy, or SIRT, with SIR-Spheres could represent a better alternative. Our decision to initiate the SARAH study was based on smaller previous studies and retrospective analyses, which suggested that SIR-Spheres could be at least as effective and was well tolerated by HCC patients," she stated.

The randomized, controlled, open-labelled SARAH (SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma) study directly compared the efficacy of selective internal radiation therapy (SIRT, or radioembolisation) using yttrium-90 [Y-90] resin microspheres (SIR-Spheres Y-90 resin microspheres, Sirtex Medical Limited, Sydney, Australia) versus sorafenib (Nexavar®, Bayer HealthCare Pharmaceuticals, Berlin, Germany).

SARAH was launched in December 2011 and concluded enrolment in February 2015.

With 459 patients treated in 25 clinical centres across France, SARAH is the largest randomized study ever to compare selective internal radiation therapy – or any liver-directed therapy – against the standard-of-care systemic therapy in the treatment of primary liver cancer. Almost 70% of the patients in the SARAH study had advanced HCC (Barcelona Clinic Liver Cancer stage C), with portal vein thrombosis and no extrahepatic spread. Most of the other patients had failed two cycles of TACE.

Results of SIR*ve*NIB, a parallel study in more than 360 Asia Pacific HCC patients will be presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago on 4 June 2017.

What is Hepatocellular Carcinoma (HCC)?

HCC patients represent 90% of all people diagnosed with primary liver cancer, which is the sixth most common cancer in the world and the second leading cause of cancer-related death. HCC affects mainly patients with cirrhosis from any cause, including viral hepatitis, alcohol misuse, and fatty liver disease, and results in more than 670,000 deaths globally each year.[2] Among people at risk of HCC, incidence of the disease increases progressively with advancing age, reaching a peak at around 70 years.[3]

Overall, one-third of patients with liver cirrhosis will develop HCC during their lifetime.[4]

- Worldwide, approximately 54% of HCC cases can be attributed to HBV infection (affecting 400 million people) while 31% can be attributed to HCV infection (affecting 170 million people).[3]
- In Africa and East Asia, the largest attributable fraction is due to HBV infection (60%), while in the developed Western world, chronic HCV infection appears to be the major risk factor.[5,6]

In addition to these causes, it is now thought that up to one in eight (12.8%) of non-alcoholic steatohepatitis (NASH) patients with cirrhosis will progress to HCC.[7] NASH – which is widely considered to be triggered by type II diabetes, insulin resistance, obesity, hyperlipidaemia and hypertension – has become the number one cause of liver disease in Western countries. Progression of NASH dramatically increases the risks of cirrhosis, liver failure, and HCC. This is thought to be related to the worldwide epidemic of diabetes and obesity.[8]

HCC occurs more often in men than women, except in Africa, where more women are affected.[2]

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).

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