

Press Release

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Fresenius Biotech presents new data on trifunctional antibody Removab[®] at 46th ASCO Annual Meeting in Chicago

- **Removab[®] shows doubling of survival in patients with early immune response**
- **Removab[®] therapy feasible in early approaches to ovarian cancer treatment**
- **New safety studies launched on second therapy cycle and 50% reduction in infusion time**

Addressing the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago (June 4-7, 2010), Fresenius Biotech presented new data from a post-hoc pivotal-trial analysis of its trifunctional antibody catumaxomab (Removab[®]). The findings show that overall survival significantly improved, more than doubling in patients who exhibit an early immune reaction subsequent to Removab[®] treatment. Such an immune response was determined in 76 percent of evaluated patients treated with Removab[®]. The data result from a correlation analysis between the primary endpoint puncture-free survival as well as the secondary clinical endpoints (overall survival, puncture-free time) and the occurrence of antibodies against Removab[®] eight days after conclusion of a four-dose intraperitoneal therapy. Results showed that patients who developed HAMAs (human anti-mouse antibodies) benefited significantly from Removab[®] therapy in all three endpoints compared to patients who did not develop these antibodies. On

average, Removab[®] patients survived 129 days and thus over twice as long as the HAMA-negative patients (p=0.0003).

Researchers observed this effect in patients treated for malignant ascites due to various epithelial cancers. "This positive correlation appears to be an essential component of the immune system's activation. In this respect, the mechanism of action differentiates Removab[®] therapy from other targeted approaches," said Dr. Diane Seimetz, Chief Scientific Officer at Fresenius Biotech.

In addition, new data and trial concepts for catumaxomab in various indications were presented in five more publications during this year's ASCO meeting: These included initial data from phase II trials in consolidation following first-line therapy, and as a perioperative approach after radical tumor surgery in ovarian cancer.

"The research findings verify the feasibility of Removab[®] therapy in early approaches to ovarian cancer treatment. We will be able to evaluate possible references to efficacy after a two-year follow-up observation of the 41 patients," said the principal trial investigator, Professor Jalid Sehouli from Charité Medical University in Berlin.

Removab[®] also was featured in two studies presented in a new ASCO poster session called "Trials in Progress." The CASIMAS study focuses on the optimization of the use and the safety profile of Removab[®]. The infusion time is reduced by 50 percent from six to three hours. An explorative SECIMAS study focuses on the safety of a second therapy cycle and is based on single-case reports according to which the antibody was well-tolerated and achieved further ascites control. SECIMAS is a roll-over study for patients who already benefited from the first cycle of Removab[®] therapy within the ongoing CASIMAS study. For the SECIMAS study, a 50 percent reduction of the infusion time from six to three hours also is applicable."

Furthermore, a recently initiated noninterventional study from Germany was presented. This research featured a prospective observational study on the application of Removab[®] under routine conditions in order to gain additional data on the antibody's systemic activity.

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The trifunctional antibody Removab® (catumaxomab)

Removab®, with its trifunctional mode of action, represents the first of a new generation of antibodies. The therapeutic objective of Removab® is to generate a stronger immune response to cancer cells that are the main cause of ascites. Removab® binds to three different cell types simultaneously: One arm of the antibody binds to the EpCAM (epithelial cell adhesion molecule) antigen in carcinoma cells, another arm binds to the CD3 molecule of T cells, and the third binds to the intact the Fc region of accessory immune effector cells (such as macrophages, monocytes, dendritic cells and natural killer cells). This simultaneous binding subsequently results in the mutual stimulation and activation of T cells and accessory cells, enabling the generation of a stronger immune response and destruction of cancer cells. Data from animal studies with trifunctional antibodies also suggest a potential long-lasting effect to prevent cancer recurrence. Removab® is under further development for various indications (e.g., gastric and ovarian cancer). Catumaxomab (Removab®) is a trifunctional antibody developed by TRION Pharma GmbH.

Removab® has been approved in the European Union since April 2009. It currently is available in Germany for treatment of malignant ascites. Fresenius Biotech is responsible for the clinical development and commercialization of Removab®.

For more information, please visit www.removab.com.

About the pivotal study

The study involved 258 patients with malignant ascites due to various carcinomas. Of those, 129 suffered from ovarian cancer, while another 129 had other types of cancer. Patients received paracentesis followed by four intraperitoneal infusions of Removab®, or paracentesis alone (control group).

The trial met its primary endpoint with high statistical significance. Patients treated with Removab® showed a median puncture-free survival (primary endpoint) of 46 days compared with 11 days in the control group ($p < 0.0001$). Puncture-free survival was defined as the period between the last Removab® infusion and the first subsequent necessary paracentesis or death, whichever occurred first. The median puncture-free time, a secondary endpoint which did not include the data from patients who died prior to subsequent paracentesis, was 77 days versus 13 days in the control group ($p < 0.0001$). A positive trend toward improved overall survival,

also a secondary endpoint, was observed for the pooled population (HR: 0.723). The subpopulation of patients treated for gastric carcinoma achieved a significantly prolonged overall survival in the Removab[®] group versus the control group (median: 71 versus 44 days, $p=0.0313$, HR: 0.469, 95% CI from 0.232 to 0.915).

The most common side effects observed during the trial, such as fever, nausea and vomiting were due to the antibody's mode of action. These side effects were predictable, generally of a minor to medium intensity, symptomatically manageable and, for the most part, transient. Most often, malignant ascites is caused by ovarian, gastric, colorectal, pancreatic, breast, endometrial and lung cancer cells.

About the post-hoc analysis

The post-hoc analysis of the pivotal study (for details, please see "About the Pivotal Study") was a correlation analysis of the immunological response and the clinical outcome after treatment with the antibody catumaxomab.

HAMAs (human anti-mouse antibodies) were measured in the patients' blood at different points in time before, during and after Removab[®] treatment. One hundred twelve of 170 patients randomized to Removab[®] treatment and 50 of 88 patients randomized to the control group were evaluated for HAMAs.

Seventy-six percent of the Removab[®]-treated patients were HAMA positive eight days after the final infusion. These patients showed a significantly longer overall survival ($p=0.0003$), time to next puncture ($p=0.0002$) and puncture-free survival ($p < 0.0001$) compared to HAMA-negative patients.

About SECIMAS

SECIMAS is a phase II study in patients with malignant ascites due to epithelial tumors. The primary objective is to evaluate the tolerance of a second intraperitoneal infusion cycle of Removab[®] (10 µg, 20 µg, 50 µg, and 150 µg). The treatment was administered over a three-hour period instead of six hours. Secondary objectives are to determine additional safety parameters, efficacy, quality of life, ascites-related symptoms and pharmacokinetics as well as pharmacodynamics. The study is currently enrolling patients in various European countries.

SECIMAS stands for "**SE**cond cycle **C**atumaxomab **I**ntraperitoneal infusion **M**alignant **A**scites **S**afety." As such, it is a roll-over study for patients with ascites control after the initial course of Removab[®] therapy within the CASIMAS study.

About CASIMAS

CASIMAS is a currently open, international study to further optimize the use and safety profile of Removab® as intraperitoneal infusions of 10 µg, 20 µg, 50 µg and 150 µg in patients with malignant ascites. These treatments also are to be administered over a three-hour period instead of six hours. The aim of this open, randomized phase IIIb study is to compare the tolerance and efficacy of the two study arms with versus without an additional 25mg prednisolon premedication. In addition, parameters for quality of life, pharmacokinetics and pharmacodynamics will be analyzed.

CASIMAS stands for “**CA**tumaxomab **S**tudy with **I**ntraperitoneal infusion in **M**alignant **A**scite**S** patients.”

About the noninterventional study (CARMA)

CARMA is an observational trial aimed to document the use of Removab® under routine clinical conditions in patients with malignant ascites due to epithelial cancers such as ovarian, breast and gastrointestinal cancers. Among others, the resulting data will be collected and analyzed by descriptive statistical methods: underlying tumor disease, demographic factors, immunological parameters, previous chemotherapeutic and/or other antibody regimen, tumor staging and clinical outcome and tolerance with regard to Removab®. The study is being conducted in Germany.

CARMA stands for “**CA**tumaxomab for the therapy of **m**alignant **a**scite**S** patients.”

About the phase II ovarian cancer trials

The first study was conducted to evaluate the safety and tolerability of intraperitoneal catumaxomab therapy in the consolidation setting for patients after radical tumor surgery and first-line chemotherapy. Forty-seven patients with advanced ovarian cancer (FIGO stage IIb-IV) with a complete response to standard chemotherapy were included in the single-arm study. Each patient received four doses (10 µg, 20 µg, 50 µg, and 150 µg, respectively) of catumaxomab by means of a three-hour infusion.

Among the 37 patients (78.7%) who received more than one infusion, 32 (86.5%) received all of the four planned infusions.

All patients experienced at least one treatment-emergent adverse event (AE), assessed as related to the study drug (731 total events). Most common AEs were nausea, pyrexia, vomiting and abdominal pain.

AEs decreased with subsequent infusions; only one patient had a grade ≥ 3 AE after the fourth infusion. Kaplan-Meier estimates of puncture-free survival and overall survival at 24 months post-treatment were 26.3% and 80.3%, respectively.

The second study was conducted to investigate the tolerability and feasibility of catumaxomab administered directly into the peritoneal cavity during radical cytoreductive surgery and postoperative standard chemotherapy with paclitaxel and platinum. Ovarian cancer patients undergoing radical surgery received one intra-operative dose (10 μg) followed by four subsequent intraperitoneal dosages (10 μg , 20 μg , 50 μg and 150 μg) of catumaxomab (as a three-hour infusion). The safety data presented are from patients who completed a one-month follow-up.

Forty-one patients (of 58 screened) were evaluable for the safety analysis. All 41 patients experienced at least one treatment-emergent adverse event (a total of 871 events). The most common adverse events were pyrexia, vomiting and abdominal pain. These were generally manageable, transient and reversible. For the most part, the observed overall profile of side effects reflects the mode of action of Removab[®].

The intra-operative application of catumaxomab is feasible. The observed postoperative complication rate was 51.2% and therefore above the 48 percent rate as defined in the protocol from a historic monocentric comparison group. This potentially higher postoperative complication rate may be associated with the immediate application of catumaxomab during radical cytoreductive surgery and may be overestimated by the methodology and design of the study.

Human anti-mouse antibodies (HAMAs)

Removab[®] (catumaxomab) is a nonhumanized mouse/rat antibody and therefore has the potential to induce anti-drug antibodies (ADAs). With regard to Removab[®], these ADAs are human anti-mouse antibodies (HAMAs). HAMAs are human immunoglobulins with specificity for mouse immunoglobulin. An immunoglobulin is a protein produced by plasma cells and lymphocytes. Immunoglobulins play an essential role in the body's own immune system.

Epithelial cell-adhesion molecule (EpCAM)

EpCAM is a tumor-associated antigen expressed on the vast majority of epithelial tumors. EpCAM is expressed on tumor cells in the majority of ascites attributed to carcinoma cells.

Malignant ascites

Malignant ascites can be caused by various kinds of tumors. Colonization of the abdominal cavity with tumor cells leads to an accumulation of fluid in the peritoneum and is associated with an unfavorable prognosis for the patient. The most common method of treatment is paracentesis, which generally must be repeated at intervals of one to two weeks and can lead to complications such as infections or elevated losses of fluids and proteins. Removab[®] destroys the peritoneal cancer cells and thus directly combats the cause of the ascites.

Fresenius is a health care group with international operations, providing products and services for dialysis, hospital and outpatient medical care. In 2009, Group sales were approximately €14.1 billion. On March 31, 2010, the Fresenius Group had 132,242 employees worldwide.

For more information, please visit www.fresenius.com.

Fresenius Biotech, a company of the Fresenius health care group, is focused on the development and marketing of biopharmaceuticals in the fields of oncology and transplantation medicine. Fresenius Biotech is headquartered in Munich, Germany.

For more information, please visit www.fresenius-biotech.com.

Removab[®] is a registered trademark of Fresenius Biotech GmbH.

TRION Pharma is a biopharmaceutical company developing trifunctional antibodies in collaboration with Fresenius Biotech. The trifunctional antibodies are produced at TRION's site in Munich, Germany.

For more information, please visit the company's website at www.trionpharma.com.

This release contains forward-looking statements that are subject to various risks and uncertainties. Future results could differ materially from those described in these forward-looking statements due to certain factors, e.g. changes in business, economic and competitive conditions, regulatory reforms, results of clinical trials, foreign exchange rate fluctuations, uncertainties in litigation or investigative proceedings, and the availability of financing. Fresenius does not undertake any responsibility to update the forward-looking statements in this release.

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