Fresenius
health care worldwide

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# Fresenius Investor News

## Secondary endpoints of phase II/III study confirm clear benefits from treatment with removab® for patients with malignant ascites

Fresenius today announced that further secondary endpoint data from a phase II/III study with removab (catumaxomab) in patients with malignant ascites confirm clear benefits for patients treated with the antibody. Trial data show that removab significantly increases time to tumor progression and has a positive influence on overall survival time. Moreover, a prolonged interval between punctures was seen in the removab group compared to the control group and this effect was also observed beyond the end of study.

The results of the randomized study include treatment data from 258 patients with malignant ascites caused by various cancers. Most patients had late-stage disease with a median life expectancy of two to three months. The primary endpoint of the study had already demonstrated that patients receiving removab had a four-fold increased puncture-free survival over a therapy with puncture alone (median 46 vs. 11 days, $p<0.0001$). The median time to the first therapeutic puncture, a key secondary endpoint, improved to 77 days in the removab group versus 13 days in the control group ($p<0.0001$). In contrast to the primary endpoint, patients who died before the next puncture were not included in this metric.

There was a clear difference between the two study arms with regard to the time to progression (TTP) of the underlying cancer. The median TTP (secondary endpoint) for the 170 patients treated with removab was 111 days, compared to 35 days for the 88 patients of the control group ($p<0.0001$). In the subgroup of patients with ascites from ovarian cancer, removab-treated TTP was also 111 days, compared to patients in the control group with 35 days ($p=0.0002$). In addition, patients with other primary cancers receiving removab also showed significant improvement in TTP, with a median of 110 days versus 34 days with puncture-therapy alone ($p<0.0001$).

A positive trend was also observed for overall survival. Median overall survival in the 170 patients in the removab group was 72 days, compared to 68 days of the 88 patients in the control group ($p=0.0846$). In a prospectively planned evaluation of 131 patients treated per protocol, a median survival advantage of 18 days was shown (removab: 86 days vs. control group: 68 days, $p=0.0085$). removab treatment also showed a positive influence on the overall survival of ovarian cancer patients

with a median survival of 110 days over 81 days for patients receiving puncture-therapy alone (p=0.1543). In patients with gastric cancer (the largest subgroup among patients with cancers other than ovarian cancer) the median survival advantage was 27 days (71 vs. 44 days, p=0.0313).

After the primary end point of the study (puncture-free survival) was reached, the data showed that puncture intervals in patients treated with removab continued to be longer than those of the patients in the control group. The intervals between the first and second puncture were 26 and 24 days in the ovarian and non-ovarian cancer group treated with removab vs. 13 and 16 days in the control group.

Secondary study endpoints and other data collected from patients after reaching the primary endpoint confirm the benefit of removab treatment for this patient group at a late stage of their disease. Collectively, the study results further indicate the efficacy of removab in the treatment of various primary cancers. "The results of the phase II/III study show clear benefits for patients being treated with removab", says Dr. Bernhard Ehmer, President Fresenius Biotech. "The results also suggest a direct antitumor effect of the trifunctional antibody. Primary and secondary endpoints as well as post study data are consistent, and demonstrate a pronounced positive trend. They all point in the right direction and this gives us confidence in our ongoing development program for ovarian and gastric cancer."

Fresenius Biotech confirms that the submission for marketing authorization with EMEA is expected in late 2007.

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## About the phase II/III study with removab

A total of 258 patients with end-stage cancer and recurrent symptomatic malignant ascites, who either no longer responded to or could no longer be treated with chemotherapy, were enrolled in this study. 129 of the patients had ovarian cancer and 129 participants had other forms of epithelial tumors (gastric 51 %, breast 10 %, pancreatic 7 %, colorectal 6 %, others 26 %). Participants in the study were randomized in a 2:1 ratio, with 170 patients randomized to treatment with removab and 88 patients to puncture therapy alone. After reaching the study endpoint 51% of patients in the control arm were also given removab (crossover). removab was administered intraperitoneally at ascending doses through infusions, following paracentesis on days 0, 3, 7, and 10. 131 patients received all four infusions of 10, 20, 50, and 150 µg.

## Mode of action of trifunctional antibody removab (catumaxomab)

The therapeutic objective of trifunctional antibodies is to generate a stronger immune reaction against tumor cells. removab has two different antigen binding sites: While one arm of the antibody recognizes and binds to T-cells, the other arm binds EpCAM (epithelial cell adhesion molecule) that is overexpressed in many types of epithelial cancers. Immune effector cells with Fc receptors (macrophages, monocytes, dendritic cells and natural killer cells) can also bind the Fc region of intact trifunctional antibodies. This simultaneous binding subsequently results in the costimulation and activation of T-cells and accessory cells, enabling the generation of a strong immune response against tumor cells. Preclinical data also suggest a potential long-lasting effect to prevent cancer recurrence. Apart from removab two other trifunctional antibodies targeting other cancer antigens are currently undergoing clinical development.

## Trifunctional Antibodies

Trifunctional antibodies are proteins that activate different cell types of the immune system simultaneously and target tumor cells specifically. Trifunctional antibodies therefore are very effective in destroying cancer cells and show a therapeutic effect even at very low doses. They are being developed by TRION Pharma GmbH.

## About Fresenius Biotech

Fresenius Biotech is a company within the Fresenius health care group and is focused on the development and marketing of biopharmaceuticals in the fields of oncology, immunology and regenerative medicine. For further information please visit www.fresenius-biotech.de.

## About Fresenius

Fresenius is a health care group with international operations, providing products and services for dialysis, hospital and outpatient medical care. In 2006, group sales were about € 10.8 billion. On December 31, 2006 the Fresenius Group had 104,872 employees worldwide. For further information please visit www.fresenius.de.

## About TRION Pharma

TRION Pharma is a biopharmaceutical company that develops and produces trifunctional antibodies based on a globally patented technology platform together with Fresenius Biotech in Munich. For further information please visit www.trionpharma.de.

## Glossary

**Puncture-free survival period:** Period between the last infusion (control group: day of the puncture) and the first subsequent necessary puncture or death, which ever occurs first.

**TTP (Time to Progression):** Time to progression is the length of time between treatment and further growth of the primary tumor or metastases.



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