NEW

Removab®
CATUMAXOMAB

PRODUCT MONOGRAPH – REMOVAB® IN MALIGNANT ASCITES

FRESENIUS BIOTECH

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Removab®
CATUMAXOMAB

TABLE OF CONTENTS

1. INTRODUCTION

Removab® (catumaxomab) is a trifunctional antibody (trAb) that is indicated for the intraperitoneal (i.p.) treatment of malignant ascites in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible. Treatment with Removab® and paracentesis has been shown to result in a clinically relevant and statistically significant improvement compared with paracentesis alone, as demonstrated by increases in puncture-free survival and time to next puncture (data on file).

Malignant ascites is the accumulation of peritoneal fluid due to the spread of malignant cells in the peritoneal cavity (peritoneal carcinomatosis). It is seen most commonly in patients with ovarian, breast, gastric, and colorectal cancer. Cancers causing malignant ascites are most often of epithelial origin. Patients with malignant ascites have a poor prognosis and currently there are no effective agents available for the treatment of malignant ascites. There is thus a high unmet medical need for effective therapies.

EpCAM (Epithelial Cell Adhesion Molecule) is a type I trans-membrane glycoprotein that is expressed in a variety of normal epithelial tissues and epithelial cancers (carcinomas), such as ovarian, gastric, lung, breast, colon, and prostate. EpCAM is involved in a number of cellular processes, e.g. cell adhesion, nuclear signaling, migration, proliferation, and differentiation. In normal epithelial tissues, EpCAM is usually shielded and therefore not accessible for antibody binding. However, due to the abnormal structure of tumor tissue, the EpCAM molecule is accessible for antibody binding in carcinomas. Since EpCAM is expressed on the vast majority of the main epithelial tumors, it is an attractive target for anti-cancer agents.

2. MALIGNANT ASCITES

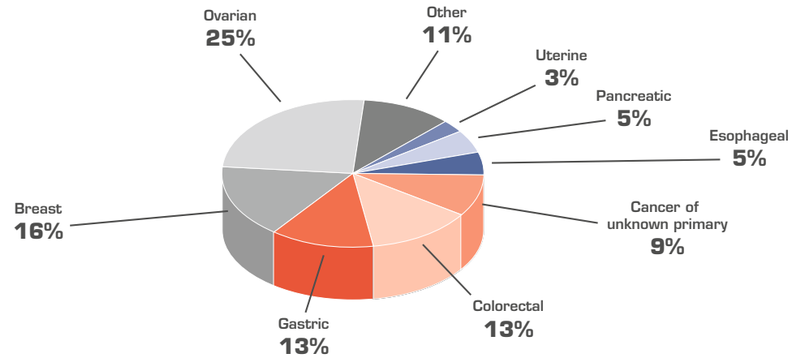
2.1 GENERAL INFORMATION

The peritoneum is a serous membrane inside the abdomen lining the abdominal wall (parietal peritoneum) and the organs (visceral peritoneum) inside the peritoneal cavity. The peritoneal space is filled with a small amount of peritoneal fluid and the space between the peritoneal membranes is covered with a fluid film that acts as a lubricant and allows the abdominal organs to glide smoothly over one another.

In healthy subjects, there is a constant movement of fluid into (influx) and out of (efflux) the peritoneal cavity. Ascites is an accumulation of excess fluid in the peritoneal cavity due to changes in both fluid influx and efflux. In the majority of cases (approximately 75 %), ascites is caused by cirrhotic liver disease, while about 10 % of cases are due to cancer, and 5 % to cardiac failure.[1] The remaining 10 % of cases are due to other causes, such as nephritic syndrome and pancreatic disease.[1]

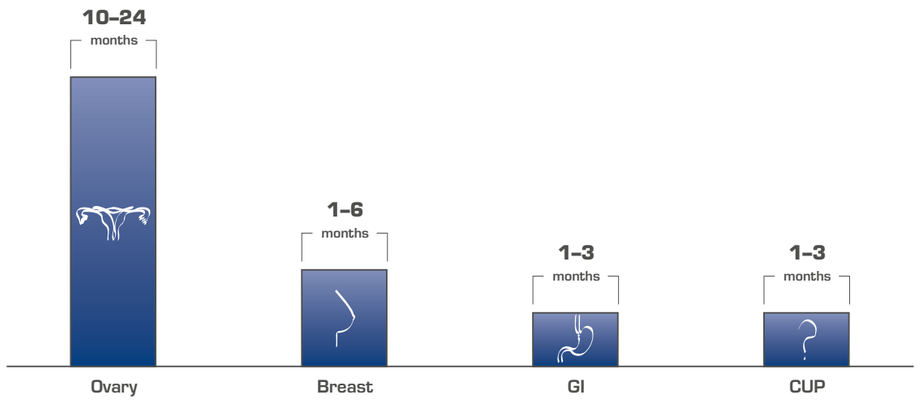
Malignant ascites is the accumulation of peritoneal fluid due to the spread of malignant cells in the peritoneal cavity (peritoneal carcinomatosis). It is seen most commonly in patients with ovarian, gastric, endometrial, breast, colon, and pancreatic cancer. Common carcinomas known to develop malignant ascites are shown in Figure 1.[2]

Figure 1. Common carcinomas that can develop malignant ascites[2]



Patients with malignant ascites have a poor prognosis with median overall survival (OS) of approximately 1–6 months.[2,3] Cancer type, low serum albumin levels, and the presence of liver metastasis are independent prognostic factors for OS.[2] For example, OS is longer in ovarian cancer compared with breast and gastrointestinal (GI) cancers and cancer of unknown primary (CUP) (Figure 2).[2,3] Symptomatic malignant ascites is associated with extreme discomfort and poor quality of life.[2]

Figure 2. Median overall survival in patients with malignant ascites by cancer type[2,3]



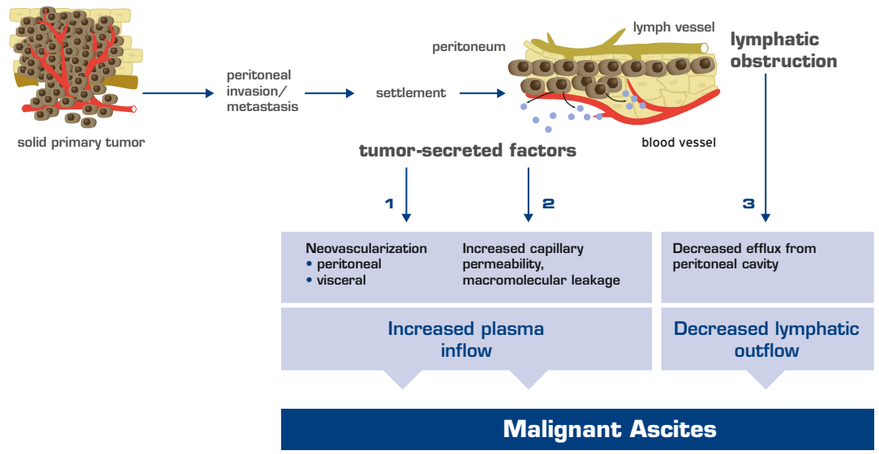
At present, there are no evidence-based guidelines for the evaluation and treatment of malignant ascites, even though it is associated with high morbidity. Chemotherapy is usually appropriate as first-line treatment for patients presenting with ascites. However, when ascites recurs, therapeutic options have been limited to palliative treatment, including puncture of the abdominal cavity (paracentesis) and systemic or i.p. chemotherapy.

2.2 PATHOPHYSIOLOGY

In general, malignant ascites develops from metastasizing tumor cells that settle and spread in the peritoneal cavity. Tumor growth eventually disrupts the normal regulation of intraperitoneal fluid flow and the maintenance of a steady state in the peritoneal cavity by simultaneously causing a greater fluid inflow as well as a reduced (lymphatic) outflow. Based on the peritoneal spread of tumor cells, there are three major mechanisms that cause flow disturbance: two cause increased fluid inflow due to tumor-related factors (1, 2) and one causes decreased outflow due to lymphatic obstruction (3) (Figure 3).[4]

1. Factors secreted by tumor cells, such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), contribute to tumor neovascularization, which is associated with higher plasma influx.
2. VEGF also causes increased permeability of the tumor capillaries and has the same effect on the capillaries of the peritoneum. Consequently, the new cancer vessels as well as the vessels of the peritoneum contribute to an increased inflow of fluid.
3. Lymphatic stomata are obstructed by tumor cells leading to a decrease in lymphatic drainage (efflux) and consequently to accumulation of fluid in the peritoneal cavity.

Figure 3. Pathophysiology of malignant ascites



2.3 DIAGNOSIS

Malignant ascites is usually diagnosed in elderly patients (median age 67 years).[2] In approximately 50 % of patients with malignant ascites, ascitic fluid is present when cancer is first diagnosed[2] and approximately 50 % of patients have symptoms related to malignant ascites at diagnosis.[2,3] Typical symptoms of malignant ascites are shown in Table 1.[2]

Table 1. Typical symptoms of malignant ascites[2]

Abdominal swelling	Fatigue
Abdominal pain	Dyspnea
Nausea	Early satiety (fullness)
Anorexia	Increased weight
Vomiting	Swollen ankles

In most cases, a physical examination is not sufficient for determining whether the ascites is due to a malignant cause or another underlying disease. A definitive diagnosis is therefore based on an analysis of the ascitic fluid, imaging diagnostics, and blood tests.[4,5]

Imaging diagnostics, e.g. computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography, can detect small amounts of fluid in the peritoneal cavity, but they cannot differentiate between a benign or malignant form of ascites. Despite this limitation, they are valuable techniques for the detection of primary tumors or metastases.[5]

The detection of tumor cells in the ascitic fluid by cytology is a highly specific indicator for a malignant cause (Figure 4). However, only about 60 % of malignant ascitic fluid samples (aspirates) are positive for tumor cells, so if malignant disease is suspected, the examination must be repeated.[6,7]

2
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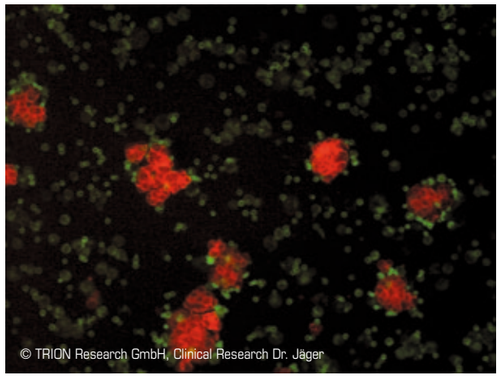
Figure 4. The detection of tumor cells in the peritoneal fluid is highly specific for the diagnosis of malignant ascites



This microscope image of the aspirate from a patient with ovarian carcinoma shows tumor cells in ascitic fluid surrounded by immune cells.

In cases of negative cancer cytology, biochemical markers in the ascites, e.g. an increased protein or lactate dehydrogenase level, or a low serum-ascites albumin gradient, may indicate a malignant cause.[4,5] Blood tests, e.g. tumor marker tests for carcinoembryonic antigen (CEA) or CA-125, may also help to identify an underlying malignancy.

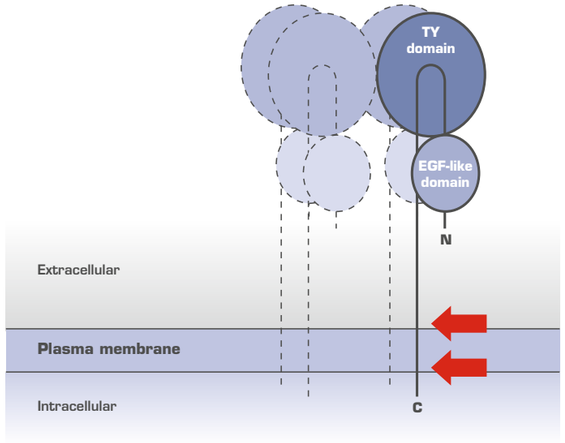
Diagnostic parameters that indicate a malignant origin for ascites are:

- Detection of tumor cells in ascitic fluid, which is the most specific proof[5,8]
- Serum-ascites albumin gradient <11 g/L[8]
- Cholesterol level >45 mg/dL[9]
- Protein level >25 g/L[8].

3. THE EPCAM ANTIGEN

EpCAM (CD326) is a type I, trans-membrane, 39–42 kDa glycoprotein that functions as a homophilic, epithelial-specific, cell-adhesion molecule.[10–12] Recently, EpCAM has been shown to be involved in additional cell processes, including nuclear signaling, migration, proliferation, and differentiation.[13,14] EpCAM, which is composed of 314 amino acids, comprises a large extra-cellular domain with an epidermal growth factor (EGF)-like domain and a putative thyroglobulin (TY) domain, a single trans-membrane region, and a short (26 amino acids) cytoplasmic tail (Figure 5).[10] EpCAM is encoded by the gene tumor-associated calcium signal transducer 1 (TACSTD1) located on the human chromosome 2p21.[15]

Figure 5. Structural model of EpCAM (adapted from Baeuerle and Gires, 2007)[10]



EpCAM is shown with an N- (N) and C-terminus (C), a trans-membrane domain, an EGF-like domain and TY repeat domain. EpCAM is depicted as a tetramer showing three additional subunits with dotted lines. The polypeptide chain is depicted with a bend within the TY domain that would orient the EGF-like domain towards the cell membrane. Cleavage sites for two proteases releasing the intracellular portion of EpCAM are indicated by red arrows.

EpCAM is expressed in a variety of normal epithelial tissues, including ovarian, gastric, lung, breast, colon, prostate, pancreas, and bile ducts.[16–18] It is found at the basolateral cell membrane of all simple, pseudostratified, and transitional epithelia, and the level of expression varies in different tissue types. Normal squamous stratified epithelia are negative for EpCAM. Additional EpCAM-negative tissues include mesothelial tissue, lymph nodes, spleen, brain, skeletal muscle, and connective tissue.[18]

In normal tissues, EpCAM is only expressed basolaterally and is shielded by tight junctions, so it is not available for binding. In contrast, in tumor tissue, EpCAM is expressed on the surface and therefore becomes available for binding.[12] EpCAM is one of the most frequently and most intensely expressed tumor-associated antigens. It is expressed in the vast majority (87–100 %) of patients with carcinomas, such as ovarian, gastric, colorectal, pancreatic, breast, and endometrial (Table 2).[16,19–21]

EpCAM is also co-expressed with the antigen CD133 on putative cancer stem cells in several carcinomas.[22–25] EpCAM-positive carcinomas maintain EpCAM expression in metastatic conditions including spreading into the peritoneal cavity.[26–29] Published data indicate that EpCAM-positive carcinoma cells are found in 71–100 % of malignant effusions (Table 2).[30–33] EpCAM screening in the pivotal phase II/III study IP-REM-AC-01 showed a similar result, with 89 % of patients having EpCAM-positive cells in the ascitic fluid (data on file). In some carcinomas, high EpCAM expression is associated with a poor prognosis.[20,21,34]

Table 2. Common carcinomas and effusions expressing EpCAM

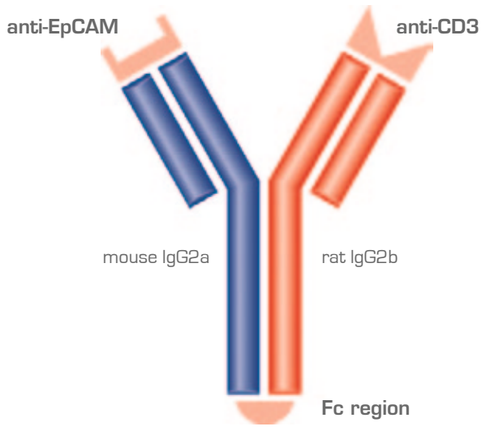
Cancer type	Percentage expressing EpCAM	Percentage of EpCAM-positive effusions
Ovarian	67–100[16,19]	79–100[30–33]
Gastric	98[20]	75–100[30,31,33]
Colon	80–100[20]	87–100[30,31,33]
Pancreatic	96[16]	83–100[30,31,33]
Breast	90[21]	71–100[30–33]
Endometrial	91–96[16]	100[31,33]

4. REMOVAB® – A TRIFUNCTIONAL ANTIBODY

4.1 STRUCTURE

Removab® (Figure 6) belongs to the family of trAbs, which combine certain characteristics of classical monoclonal antibodies (mAbs) and were developed to improve the potency of therapeutic Abs. In contrast to conventional mAbs, which have two identical binding arms, trAbs have two different antigen-binding arms.

Figure 6. Structure of Removab®



The two different specificities of the trAb antigen-binding sites enable simultaneous recognition of two cell types: tumor cells and T-cells. In addition, the functional Fc domain can simultaneously recruit and activate Fcγ receptor (FcγR)-positive accessory cells (e.g. macrophages, natural killer [NK] cells, and dendritic cells [DCs]) leading to a complex immune reaction against the tumor cells.[35–37]

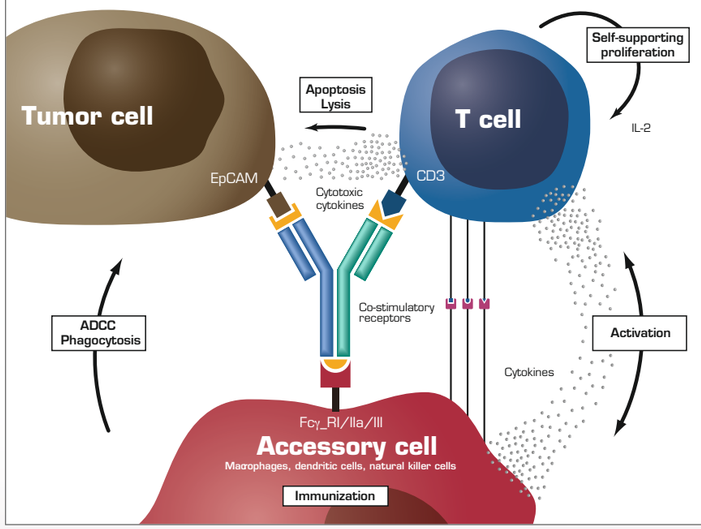
4.2 MECHANISM OF ACTION

The postulated mechanism of action of Removab® is shown in Figure 7 and Table 3. Removab® binds to three different cell types:

- Tumor cells (EpCAM)
- T-cells (CD3)
- Accessory cells expressing FcγRs, e.g. macrophages, NK cells, and DCs.

This is postulated to result in a tricell complex: binding of Removab® to EpCAM-positive tumor cells, T-cells, and accessory cells results in the simultaneous recruitment and activation of different types of immune-effector cells at the tumor-cell site. The tumor cells and immune-effector cells are brought into close proximity and a complex 'crosstalk' between T-cells and accessory cells can occur. This 'crosstalk' includes the cytokines and co-stimulatory signaling necessary for the physiological activation of the T-cell cascade, which results in efficient killing of tumor cells (Figure 7).

Figure 7. The postulated mechanism of action of Removab®



Co-stimulatory receptors: e.g. CD40, CD40L, B7.1-2, CD28, CD2, LFA-3
Cytokines: e.g. IL-1, IL-2, IL-6, IL-12, TNF-α, IFN-γ, DC-CK1, GM-CSF

ADCC=antibody-dependent, cell-mediated cytotoxicity; DC=dendritic cell; DC-CK=dendritic cell cytokine; GM-CSF=granulocyte monocyte colony stimulating factor; IL=interleukin; IFN=interferon; TNF=tumor necrosis factor

The interaction of different immune effector cells at the tumor-cell site results in efficient elimination of tumor cells by several killing mechanisms:

- T-cell-mediated lysis through perforin- and/or granzyme-B-driven mechanisms[38]
- Phagocytosis[35,36]
- Antibody-dependent, cell-mediated cytotoxicity (ADCC) following activation of Fcγ RIII-positive accessory cells[35]
- Cytokines, such as tumor necrosis factor (TNF)-α and interferon (IFN)-γ [39,40] which contribute to the anti-tumor activity of Removab®.

The induction of anti-tumor immunity has been shown following treatment with BiLu (anti-human EpCAM x anti-mouse CD3) in preclinical studies in mice using syngeneic mouse tumors transfected with a gene coding for human EpCAM.[37]

Table 3. Mechanism of action: immunological mechanisms induced by Removab®

Simultaneous recruitment of T-cells and accessory cells to the tumor site and concerted activation at the tumor site		**Improved tumor-cell elimination** (e.g. apoptosis-resistant tumor cells) **by different killing mechanisms mediated by T-cells** (perforin-/granzyme-B-dependent lysis, cytokine release [e.g. TNF-α and IFN-γ]) **and accessory cells** (phagocytosis, ADCC, and cytokine release) contributes to anti-tumor activity
Preferential **binding and activation of type I, IIa and III Fcγ R-positive accessory cells**, e.g. macrophages and DCs, but no or only marginal binding to Fcγ R IIb		
• Physiological **co-stimulation of T-cells by activated accessory cells** in the tricell complex • Thus, **T-cell anergy** caused by non-physiological activation via CD3 alone **can be avoided** • Co-stimulation and interleukin (IL)-2 secretion leads to **physiological T-cell proliferation and differentiation**		

4.3 APPROVED INDICATION

Removab® is indicated for the i.p. treatment of malignant ascites in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

4.4 RATIONALE FOR USE OF REMOVAB® IN MALIGNANT ASCITES DUE TO CARCINOMAS

- EpCAM is expressed on the vast majority of the main carcinomas that cause malignant ascites.
- EpCAM is expressed on tumor cells in the majority of malignant effusions due to carcinomas.
- The inner layer of the peritoneum consists of mesothelial cells, so the environment within the peritoneal cavity is EpCAM-negative since mesothelial cells do not express EpCAM on their surface.
- Removab® applied to the peritoneal cavity of patients with malignant ascites specifically targets epithelial tumor cells, but not normal tissue.

5. REMOVAB® PHARMACOLOGY

5.1 PRECLINICAL EVIDENCE FOR ANTI-TUMOR EFFICACY

Due to the specificity of Removab® for its human target antigens, the full pharmacological activity cannot be achieved in standard animal models, including non-human primates. Therefore, a targeted preclinical testing strategy was developed to obtain relevant information from scientifically justified, pharmacological model systems.

The trifunctional mechanism of action of Removab® relies on the concerted physiological activation of T-cells and accessory immune cells at the tumor site, which results in concerted anti-tumor activity.

This mechanism of action has been deduced from pharmacodynamic experiments that include specific binding to target cells, T-cells, and accessory cells, and their activation. Removab® effectively eliminated target carcinoma cells with high to low EpCAM expression *in vitro*, independent of the cancer type. The effects mediated by Removab® were found to be superior compared to its parental monospecific antibody (HO-3, anti-EpCAM): Removab® was about 1000-fold more effective.[41]

Pharmacodynamic studies *in vitro* also demonstrated further mechanisms that contribute to the anti-tumor response mediated by Removab®. Perforin-mediated lysis and granzyme-B release contribute to the Removab®-induced elimination of tumor cells. Macrophages eliminate tumor cells by antibody-dependent cellular phagocytosis (ADCP) that is dependent on EpCAM expression by the target tumor cells. High local concentrations of Removab® can activate human complement, which may also contribute to the anti-tumor activity of Removab®. The efficacy of Removab® was also demonstrated in more complex three-dimensional *in vitro* models (spheroids) that closely resemble the pathophysiological *in vivo* situation in tumor micro-regions and micro-metastases.[42,43]

The *in vivo* anti-tumor activity of Removab® was confirmed in an immunologically compromised murine model of ovarian carcinoma. *In vivo* efficacy and induction of long-lasting anti-tumor immunity in two mouse tumors was demonstrated using the variant antibody BiLu (anti-mouse CD3 x anti-human EpCAM), which has an equivalent structure to Removab® but binds to mouse CD3. BiLu was used to demonstrate proof of concept *in vivo* and was highly active in terms of survival (100 % survivors). In addition, a long-lasting anti-tumor immunity was induced in these mice by BiLu.[37]

These results are in line with a specific localization and prolonged accumulation of Removab® in EpCAM-positive tumor xenografts in SCID mice.

The results of *in vitro* drug-interaction studies suggest that prednisolone, at a concentration which corresponds to a clinical dose of 25 mg, led to a reduction of Removab®-induced cytokine release, but the anti-tumor activity of Removab® *in vitro* was maintained. In contrast, dexamethasone, used to control cytokine release, may reduce the anti-tumor efficacy of Removab®.

5.2 PRECLINICAL SAFETY AND TOXICITY DATA

Due to the specificity of Removab® for its human target antigens, a tailored set of experiments was conducted. T-cell activation and cytokine release observed *in vitro* and in patients in response to Removab® are part of the anti-tumor response and a key feature of its mechanism of action. Cytokine release is responsible for adverse events in the clinical setting and elevated systemic cytokine levels have been observed after i.p. administration of Removab®.

Clinical findings of a transient decrease in peripheral blood lymphocyte counts are consistent with observations in mice after administration of BiLu (binding to mouse CD3). In this preclinical model, lymphocyte counts returned to normal levels after 48 hours. This very short recovery interval argues against an antibody-mediated destruction of lymphocytes. It is more likely an antibody-induced adhesion and migration of T-cells out of the blood stream into the tissues and possibly the tumor, due to cytokine effects on lymphocytes and the endothelium; an effect that is well-described.[44]

Binding of Removab® to normal human tissue observed *in vitro* does not allow its tissue distribution to be predicted *in vivo*. Since EpCAM in normal tissues is shielded, it is generally not accessible for Removab® binding under physiological conditions. In contrast to normal tissues, EpCAM on tumor cells is accessible for binding. Moreover, the transfer of Removab® into solid tumors is possible because tumor blood vessels are generally leaky and have a higher permeability for macromolecules than normal vessels.

Toxicity data obtained in standard animal models (including the monkey) are of limited significance for humans due to the absence of binding of Removab® to EpCAM and CD3 in these animal models.

Administration of Removab® in standard animal models (mouse, rat, rabbit, guinea pig, and cynomolgus monkey) did not result in abnormal or test-substance-related acute toxicity or local intolerance at the administration site. The antigenicity and immunotoxicity of Removab® were investigated in the cynomolgus monkey. No immunotoxic effects were observed following intravenous infusion of Removab® and there was no effect on circulating levels of cytokines or complement. The detection of anti-drug antibodies (ADAs) in the monkey was expected since Removab® (mouse/rat bispecific antibody) is recognized as a foreign (immunogenic) molecule by the animal's immune system.

5.3 CLINICAL PHARMACODYNAMICS

In vivo pharmacodynamic results

The mechanism of action, including cellular and humoral interactions, was investigated by monitoring patients' ascitic fluid and peripheral blood after i.p. administration of Removab®. Analyses were performed during the pivotal phase II/III study IP-REM-AC-01 (Table 6, page 27) and during the study IP-REM-PK-01-EU for the following parameters:

- Number of EpCAM-positive tumor cells in malignant ascites
- Ratio between EpCAM-positive tumor cells and CD45-positive leukocytes
- VEGF concentration in malignant ascites
- Expression of the T-cell-activation marker CD69
- Systemic cytokine levels

Pharmacodynamic data obtained during and after Removab® therapy indicate that efficacy is based on the proposed mechanism of action.

- Tumor cells considered to be the main cause of malignant ascites were efficiently eliminated after administration of Removab® *in vivo* (to a median of zero, 24 hours after the last infusion).
- Tumor-cell depletion was associated with a statistically significant decrease in VEGF concentration in the ascitic fluid during and after Removab® treatment, confirming the elimination of tumor cells in the peritoneal cavity.
- The number of leukocytes (CD45-positive cells) in the ascitic fluid showed a distinct increase during and after treatment with Removab®, leading to a pronounced decrease in the ratio between EpCAM-positive tumor cells and CD45-positive cells.
- The percentage of activated immune effector cells (CD69-positive T-cells) within the leukocyte population was increased.
- An additional indicator of a Removab®-induced immune reaction was an increase in cytokine serum levels, which were observed after Removab® infusions.

In vitro pharmacodynamic results

Ascites samples collected before treatment were incubated with Removab® *in vitro* to evaluate the potential of the patient's immune system to react against tumor cells.

- A decrease in EpCAM-positive tumor cells was observed in ascites samples incubated *in vitro* in the presence of Removab®.
- The percentage of activated immune effector cells, e.g. CD69-positive T-cells in ascites samples, was increased after *in vitro* incubation with Removab®.
- Concentrations of cytokines (IL-2, IL-4, IL-6, IL-10, IFN-γ, and TNF-α) were increased in the supernatants of ascites samples incubated with Removab®.

5.4 IMMUNOGENICITY

As Removab® is a non-humanized mouse/rat antibody, the development of antibodies against Removab® was expected after treatment with Removab®. However, since Removab®-induced ADAs, i.e. human anti-mouse antibodies (HAMAs) and human anti-rat antibodies (HARAs), generally develop after the treatment period, no interference with Removab® was expected and observed using the current clinical treatment regimen.

Before treatment with Removab®, all patients were ADA negative. In the pivotal study IP-REM-AC-01, only 6 % (7/124) of patients treated with Removab® developed ADAs in serum before the fourth infusion. There was no apparent relationship between the puncture-free survival time (range, 8–121 days) and the presence of ADAs in these patients. In addition, the adverse-event profile of Removab® in these seven patients with early ADAs was consistent with that for the overall patient population. A reversed ADA pattern was observed 1 month after the fourth infusion of Removab®, when most patients had become ADA positive (94 % of patients).

Co-culture studies *in vitro* showed that ADA-positive serum from patients treated with Removab® resulted in a concentration-dependent inhibition of Removab® binding to target cells *in vitro* and inhibition of the *in vitro* anti-tumor activity of Removab®. ADAs also inhibited cytokine release from peripheral blood mononuclear cells (PBMCs) induced by Removab® in preclinical *in vitro* studies.

5.5 PHARMACOKINETICS

Pharmacokinetic data are available from study IP-REM-PK-01-EU in which four i.p. Removab® infusions of 10, 20, 50, and 150 µg were investigated in 13 patients with symptomatic malignant ascites due to EpCAM-positive carcinomas.

Removab® concentrations in ascitic fluid

The highest concentrations of Removab® were detected in the ascitic fluid, i.e. at the place of intended efficacy. The concentrations increased with the number of infusions and the doses applied in most patients.

Removab® concentrations in plasma

After the third and fourth i.p administration, Removab® could also be detected in plasma, showing systemic availability. In most patients, there was a delayed increase in plasma concentration after i.p. administration of Removab® and, after reaching a maximum, a decrease was observed. The main pharmacokinetic parameters in plasma are shown in Table 4.

Table 4. Pharmacokinetic parameters of Removab® in plasma

Geometric mean plasma C_{max}	**0.5 ng/mL** (range, 0–2.3)
Geometric mean plasma AUC	**1.7 day* ng/mL** (range, <LLoQ–13.5)
Geometric mean apparent terminal plasma elimination half-life ($t_{1/2}$)	**2.5 days** (range, 0.7–17)

LLoQ = Lower limit of quantification

Correlation of systemic exposure and cytokine concentrations, as well as clinical findings, did not show any apparent relationship. Thus, systemic exposure determined after i.p. administration of Removab® does not raise any safety concerns.

The inter-patient variability of pharmacokinetic parameters was high. This is expected considering the route of administration and the varying amount of unbound Removab® that is available for systemic entry due to different degrees of tumor burden, number of immune effector cells in the ascitic fluid, and the diseased peritoneum. This explanation is supported by preclinical data obtained in a SCID mouse model showing that the systemic concentration of Removab® after i.p administration is dependent on the number of binding partners (EpCAM-positive cells and CD3-positive cells) in the peritoneal cavity.

5.6 DOSE RATIONALE

The dose regimen consists of a single treatment cycle of four i.p. infusions at doses of 10 µg on day 0, 20 µg on day 3, 50 µg on day 7, and 150 µg on day 10. This dose schedule was defined as the standard dose based on the results of two phase I/II studies to determine the maximum tolerated dose (MTD) (STP-REM-01 in malignant ascites and IP-REM-PC-01-DE in peritoneal carcinomatosis). The scheme of ascending doses was selected based on the facts that i.p. administration of Removab® is associated with symptoms attributed to cytokine release and that patients did not tolerate high starting doses. The increased doses of Removab® in subsequent infusions were generally well tolerated. The dose schedule is based on the following considerations.

First i.p. dose of 10 µg

- The anti-tumor activity of Removab® against epithelial human tumor cell lines from different tissues that express high to low levels of EpCAM was already seen at Removab® concentrations of <10 ng/mL *in vitro*.
- In the phase I/II dose-finding studies STP-REM-01 and IP-REM-PC-01-DE, the starting dose of 10 µg Removab® was well tolerated, with only moderate and fully reversible symptoms attributed to systemic cytokine release.

Second i.p. dose of 20 µg

- A dose of 50 µg was tested in three patients (study STP-REM-01: dose level IIa) as the second dose. However, due to a reversible bilirubin elevation of Common Terminology Criteria of Adverse Events (CTCAE) grade 3 in one of three patients, the second dose was reduced to 20 µg as a precaution.
- The data indicate that low doses should be applied at the first and second infusion to minimize the risk for strong initial reactions, especially those associated with systemic cytokine release.

Third i.p. dose of 50 µg

- In study STP-REM-01, the third dose was set at 50 µg. This dose was well tolerated and no safety concerns were raised. Therefore, the dose was maintained in subsequent dose groups.
- In study IP-REM-PC-01-DE, the third dose was escalated to 100 µg. However, at this dose level, two dose-limiting toxicities (DLTs, both cytokine-release-related symptoms) in two of three patients were observed, indicating that patients do not tolerate a dose escalation above 50 µg as the third dose.

Fourth i.p. dose of 150 µg

- In study STP-REM-01, a serious adverse event occurred at the fourth dose of 200 µg on day 10 (bowel obstruction), although this was not a DLT and the MTD in this study was defined as 10, 20, 50, and 200 µg. However, a decision was taken to reduce the fourth dose to 150 µg in order to define a robust and safe application schedule for subsequent studies.

The interval between infusions was selected to allow patients sufficient time to recover from symptoms and laboratory abnormalities following each infusion and also for the immune system to recover. The recommended infusion time is 6 hours.

6. REMOVAB® CLINICAL EFFICACY IN MALIGNANT ASCITES

The clinical efficacy of Removab® in the treatment of malignant ascites has been demonstrated in two clinical studies (Table 5).[45,46]

Table 5. Clinical studies in malignant ascites

Study number	Indication	Phase	Study design	N	Reference
STP-REM-01	Malignant ascites due to ovarian cancer	I/II	Multicenter, multinational, uncontrolled, open-label, sequential, dose-escalating study	23	45
IP-REM-AC-01	Malignant ascites due to EpCAM-positive cancer	II/III	Multicenter, multinational, two-arm, randomized (2:1) to paracentesis plus Removab® or paracentesis alone (control), open-label study Patients were stratified according to cancer type: ovarian or non-ovarian cancer	258 (129 [85 Removab® and 44 control] in each stratum)	46

6.1 PHASE I/II STUDY (STP-REM-01)

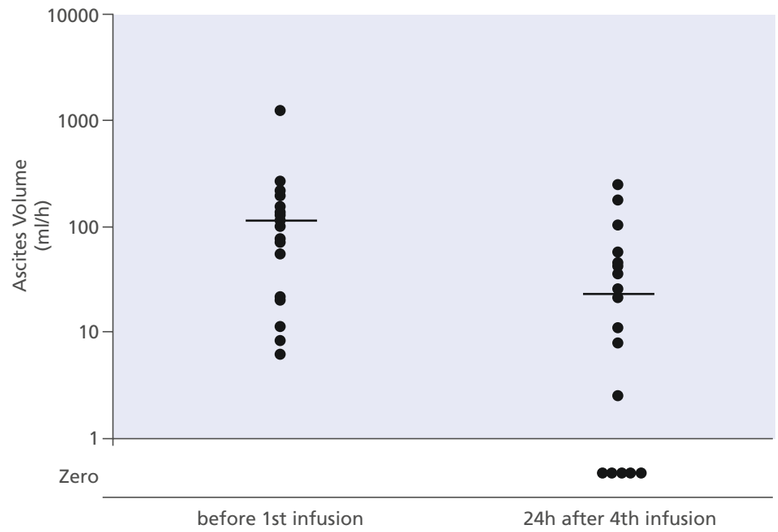
This open-label, phase I/II, dose-escalation study was conducted to investigate the tolerability and efficacy of i.p. Removab® and to identify the MTD in patients with malignant ascites due to ovarian cancer.[45] Twenty-three women (median age, 61.7 years; range, 42–80) with recurrent ascites due to treatment-refractory ovarian cancer were treated with four or five 6-hour Removab® i.p. infusions at doses of 5–200 µg on days 0, 3, 6, and 9 for the first four dose groups and a fifth infusion on day 13 for the fifth dose group.

At study inclusion, patients had advanced and heavily pretreated disease with a median of three prior medical cancer treatments (range, 1–8) and a median time of 24 months (range, 1–103) from diagnosis. At primary diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage was IIIb in two (9 %), IIIc in 14 (61 %), and IV in seven (30 %) patients.

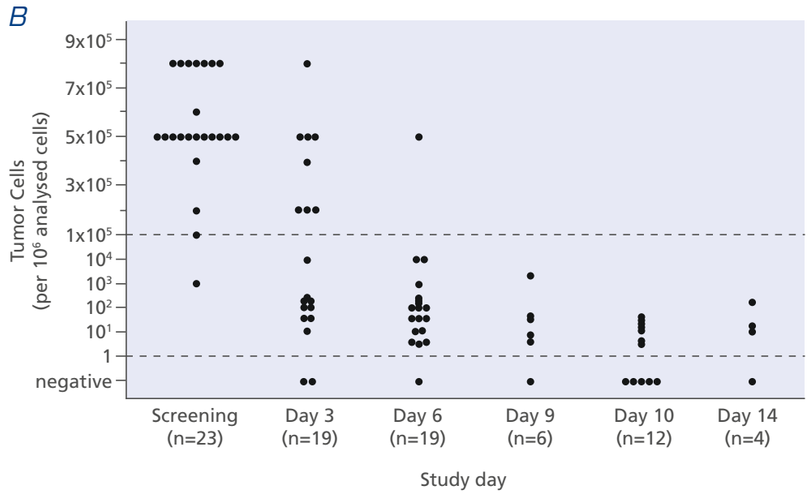
Removab® treatment resulted in a significant and sustained reduction of ascites flow rate (Figure 8A). Mean and median ascites flow rates were comparable in all dose groups at baseline (range, 46.2–446.9 mL/hour) and decreased from a median of 105 mL/hour at baseline to 23 mL/hour one day after the fourth infusion, resulting in a median decrease of 52 mL/hour. Twenty-two of 23 patients did not require paracentesis between the last infusion and the end of study at day 37.

Figure 8. Reduction of ascites flow and number of tumor cells in the ascitic fluid during i.p. therapy with Removab®[45]

A



Individual ascites flow rates in the 17 patients of dose groups IIb, III, IV, and V, before treatment and 24 hours after the fourth antibody infusion. Lines over the dots, median values of 105 and 23 mL/hour, respectively.



EpCAM-positive tumor cells in ascites per 10^6 immunohistochemically analyzed cells in ascites. Days 3, 6, and 9 before the second, third, and fourth infusion. Days 10 and 14, 1 day after the fourth and fifth infusion.

Tumor cell-count monitoring revealed a reduction of EpCAM-positive malignant cells in ascites by up to 5 logs (Figure 8B). The mean value of EpCAM-positive tumor cells was reduced from 539,000 per 10^6 analyzed cells before treatment to 39 per 10^6 analyzed cells at the last measurement, resulting in a mean reduction of 99.9 %. In six of 23 patients, tumor cells were eliminated to levels below the detection limit.[45] The MTD was defined as 10, 20, 50, 200, and 200 µg for the first to fifth doses.

6.2 PIVOTAL PHASE II/III STUDY (IP-REM-AC-01)

This study (Table 6) was designed to assess the efficacy and safety of Removab® in the treatment of malignant ascites due to carcinoma.[46]

Table 6. Study IP-REM-AC-01[46]

Study title	Two-arm, randomized (2:1), open-label, phase II/III study in EpCAM-positive cancer patients with symptomatic malignant ascites using paracentesis plus the trifunctional antibody Removab® (anti-EpCAM x anti-CD3) versus paracentesis alone
Patients	Patients were stratified according to cancer type: ovarian or non-ovarian N = 258 129 ovarian cancer: 85 Removab®, 44 control 129 non-ovarian cancer: 85 Removab®, 44 control
Primary endpoint	Puncture-free survival Defined as time after day 0 (control group)/1 day after last infusion (Removab® group) to first need for therapeutic paracentesis or death, whichever occurred first
Secondary endpoints	• Time to next paracentesis • Tumor-cell load in ascitic fluid • OS • Time to progression (TTP)
Number of centers/countries	53/13

Patients with recurrent symptomatic malignant ascites resistant to conventional chemotherapy were randomized to treatment with Removab® plus paracentesis or paracentesis alone (control group) and stratified by cancer type. Removab® was administered as four 6-hour i.p. infusions on days 0, 3, 7, and 10 at doses of 10, 20, 50, and 150 µg, respectively. Patients in the control group who fulfilled the eligibility criteria and had two therapeutic punctures after day 0 were permitted to receive Removab® in a subsequent single-arm, crossover period.

Results

Puncture-free survival was statistically significantly longer for Removab® plus paracentesis than paracentesis alone in the intent-to-treat (ITT) population (Table 7 and Figure 9A). The hazard ratio (HR) for the pooled population corresponded to a risk reduction for puncture or death of 74.6%.

Table 7. Puncture-free survival and time to next paracentesis[46]

	Pooled population (n=258)		**Ovarian cancer (n=129)**		**Non-ovarian cancer (n=29)**		**Gastric cancer (n=66)**	
	R+P (n=170)	P (n=88)	R+P (n=85)	P (n=44)	R+P (n=85)	P (n=44)	R+P (n=46)	P (n=20)
Puncture-free survival (days) Median (95% CI)	46 (35,53)	11 (9, 16)	52 (38, 62)	11 (9, 20)	37 (27, 49)	14 (8, 17)	44 (27, 69)	15 (8, 21)
Factor of prolongation p-value* HR, estimate (95% CI)	4.2 <0.0001 0.254 (0.185, 0.350)		4.7 <0.0001 0.205 (0.129, 0.327)		2.6 <0.0001 0.309 (0.199, 0.482)		2.9 <0.0001 0.289 (0.151, 0.554)	
Time to next paracentesis (days) Median (95% CI)	77 (62, 104)	13 (9, 17)	71 (52, 104)	11 (9, 20)	80 (64, 135)	15 (8, 19)	118 (64, 147)	15 (8, 24)
Factor of prolongation p-value* HR, estimate (95% CI)	5.9 <0.0001 0.169 (0.114, 0.251)		6.4 <0.0001 0.152 (0.088, 0.260)		5.3 <0.0001 0.183 (0.101, 0.331)		7.9 <0.0001 0.143 (0.057, 0.359)	

The median time to the next therapeutic paracentesis was distinctly longer for Removab® plus paracentesis than paracentesis alone (Table 7): pooled population, 77 versus 13 days (Figure 9B); ovarian cancer, 71 versus 11 days; non-ovarian cancer, 80 versus 15 days (all p<0.0001). The prolonged time to the next paracentesis with catumaxomab correlates to a saving of approximately five punctures. A comparison of patients who received Removab® during the crossover period with their time as control patients in the randomized part of the study showed that the time to next therapeutic paracentesis was extended by a median of 33 (ovarian) and 50 (non-ovarian) days.

6
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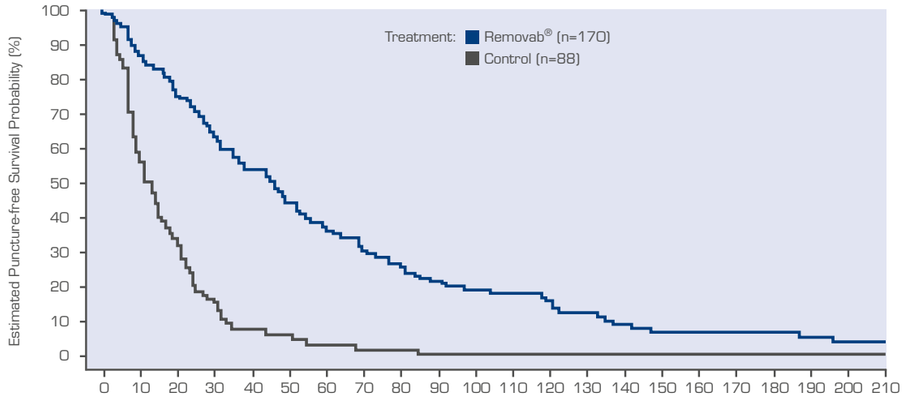
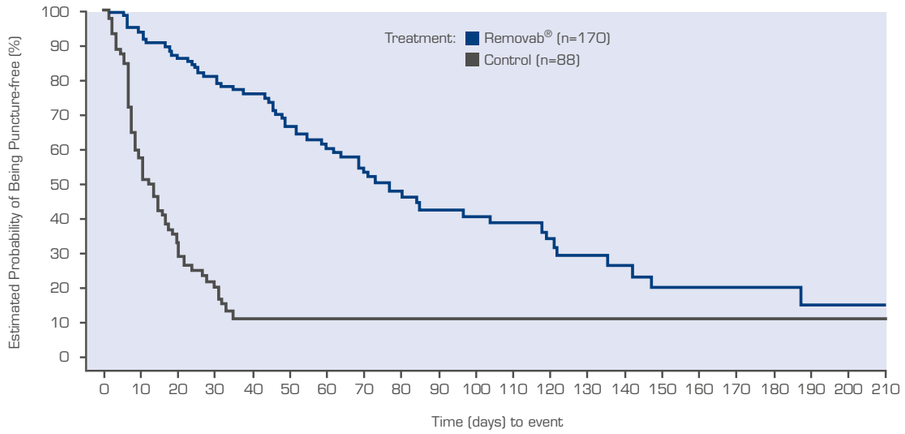
Figure 9. Kaplan-Meier estimates of puncture-free survival and time to next paracentesis, in the pooled population.

A: Puncture-free survival



B: Time to next paracentesis



Although the study was not powered or designed to detect statistically significant differences in OS, there was a positive trend in favor of catumaxomab versus paracentesis alone, as shown by the HR: pooled population 0.723 (median 72 versus 68 days); ovarian cancer 0.650 (median 110 versus 81 days); and non-ovarian cancer 0.825 (52 versus 49 days). In the subgroup of gastric cancer patients, a statistically significant prolongation of OS was observed for catumaxomab versus paracentesis alone (71 versus 44 days, p=0.0313, HR 0.469).[46] The results are shown in Table 8.

Table 8. Overall survival[46]

	Ovarian cancer	Non-ovarian cancer	Gastric cancer	Pooled population
Removab® Median (95 % CI), days 6-month survival rate (%) 1-year survival rate (%)	110 (70, 164) 38.3 20.5	52 (44, 74) 17.2 2.6	71 (50, 98) 17.3 2.5	72 (61, 98) 27.5 11.4
Control Median (95 % CI), days 6-month survival rate (%) 1-year survival rate (%)	81 (68, 134) 9.0 9.0	49 (33, 68) 4.9 0	44 (28, 68) 0 0	68 (49, 81) 6.7 3.4
p-value (log-rank test)	0.1543	0.4226	0.0313	0.0846
Hazard ratio (95 % CI)	0.650 (0.357, 1.183)	0.825 (0.514, 1.324)	0.469 (0.232, 0.951)	0.723 (0.498, 1.048)

As catumaxomab is a non-humanized chimeric antibody derived from mouse/rat IgG, it is potentially immunogenic when administered to humans. Thus, the development of ADAs against the murine and rat components of the antibody molecule is to be expected. In clinical studies, almost all patients treated with catumaxomab developed HAMAs and HARAs.

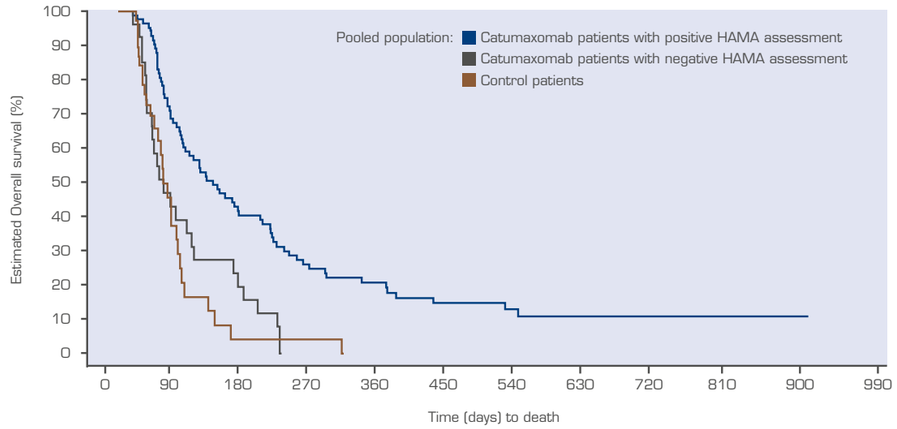
Data from the pivotal study IP-REM-AC-01 were analyzed to investigate a possible relationship between HAMA positivity (Medac test) and clinical outcome (puncture-free survival, time to first puncture, and OS) in catumaxomab-treated patients.[47] The statistical analysis was based on the data from visit 6, which was performed 8 days after the fourth infusion of catumaxomab.

Table 9. Median time to puncture-free survival, time to first puncture and OS in catumaxomab-treated patients with positive and negative HAMA titers 8 days after the last catumaxomab infusion and patients in the control group (pooled population)[47]

	Control	Catumaxomab		Group comparison	
	(n=50)	HAMA negative (n=27)	HAMA positive (n=85)	Control versus HAMA negative	HAMA positive versus HAMA negative
	Median (days)				
PFS	21	27	64	p=0.0327	p<0.0001
TTFP	21	46	104	p=0.0045	p=0.0002
OS	62	64	129	p=0.4009	p=0.0003

OS = overall survival; PFS = puncture-free survival, TTFP = time to first puncture

Figure 10. Overall survival in HAMA-positive and HAMA-negative patients*[47]



*Patients were assessed 8 days after the last catumaxomab infusion or 8 days after paracentesis (control)

Puncture-free survival was significantly longer in HAMA-positive patients versus HAMA-negative patients (64 versus 27 days, p<0.0001) (Table 9). A significant benefit for HAMA-positive patients was also shown for time to first puncture (104 versus 46 days, p=0.0002), and for OS (129 versus 64 days, p=0.0003) (Table 9, Figure 10). When comparing HAMA-negative patients in the catumaxomab arm with control patients, superior results for catumaxomab treatment were observed for time to first puncture (46 versus 21 days, p=0.0045) and puncture-free survival (27 versus 21 days, p=0.0327), but not for OS (64 versus 62 days, p=0.4009).

In conclusion, Removab® administered as a sequence of four i.p. infusions of 10, 20, 50, and 150 µg resulted in a clear clinical benefit in the treatment of carcinoma patients with symptomatic malignant ascites.

7. REMOVAB® CLINICAL SAFETY

The safety profile of Removab® is based on a pooled analysis of adverse events from five completed studies: IP-REM-AC-01, STP-REM-01, IP-REM-PC-01-DE, AGO-Ovar-2.10, and IP-REM-PK-01-EU. A total of 258 patients were treated in these studies using i.p. administration of Removab® and 207 (80 %) patients completed treatment, underlining the good tolerability of the drug.

Adverse events (AEs) are defined as all untoward signs and symptoms observed in study patients regardless of a causal relationship to Removab®. Adverse drug reactions (ADRs) are defined as AEs considered causally related to Removab®. Both AEs and ADRs were graded for severity according to the CTCAE grades: grade 1, mild; grade 2, moderate; grade 3, severe; and grade 4, life-threatening.

Most of the ADRs observed during/after Removab® treatment reflect its mechanism of action. Therefore, the risks of Removab® treatment are generally predictable and manageable. Removab® may cause symptoms related to local and systemic cytokine release, a feature that is common with mAbs in current use. Common ADRs include those most probably caused by a release of cytokines (fever, nausea, and vomiting) or due to the i.p. route of administration (abdominal pain). The most frequent symptomatic grade 3 ADRs were abdominal pain, pyrexia, fatigue, and nausea/vomiting. Grade 4 ADRs were isolated cases and mostly related to progression of the underlying malignant disease, such as ileus.

7.1 ALL ADVERSE EVENTS

Over 98 % of patients experienced at least one AE. Among the most common AEs were pyrexia, nausea, and vomiting, which are assumed to be caused by the release of cytokines. The second most common AE was abdominal pain, which is partly considered an effect of peritoneal irritation due to paracentesis and i.p. infusion. Most events were of mild to moderate intensity.

The majority of AEs were transient and usually resolved without sequelae within several days or a few weeks. There was no distinctive pattern of AEs corresponding to specific infusions. Although the proportion of patients with AEs was slightly higher after the first and third infusions than after the second and fourth infusions, there was no distinctive pattern of AEs corresponding to specific infusions. The most common AEs in general (pyrexia, abdominal pain, nausea, and vomiting) were similarly reported AEs after all infusions.

7.2 ADVERSE EVENTS OF CTCAE GRADE 3/4*

Overall, 255 patients (99 %) had at least one AE (all grades), whereas 176 patients (68 %) had at least one AE of grade 3/4. Abdominal pain, nausea/vomiting, pyrexia, and fatigue were the most common symptomatic grade 3/4 AEs (Table 10).

Table 10. Main adverse events of CTCAE grade 3/4 (N=258)

Adverse event	Grade 3, n (%)	Grade 4, n (%)
Abdominal pain	32 (12)	–
Vomiting	16 (6)	–
Pyrexia	13 (5)	–
Fatigue	10 (4)	–
Nausea	10 (4)	–
Anorexia	9 (3)	–
Pleural effusion	7 (3)	2 (<1)
Anemia	–	1 (<1)

*Excluding adverse events exclusively related to the underlying malignant disease

7.3 ADVERSE DRUG REACTIONS

Overall, 233 patients (90 %) had at least one ADR (all grades) and 127 patients (49 %) had at least one symptomatic ADR of grade 3/4 (Table 11). Abdominal pain, pyrexia, and vomiting were the most common symptomatic grade 3 ADRs. Grade 4 ADRs were isolated cases mostly related to progression of the underlying malignant disease, such as ileus.

Table 11. Main symptomatic adverse drug reactions of CTCAE grade 3/4 (N=258)

Adverse event	Grade 3, n (%)	Grade 4, n (%)
Abdominal pain	25 (10)	–
Pyrexia	13 (5)	–
Vomiting	10 (4)	–
Ileus	3 (1)	3 (1)
Nausea	6 (2)	–
Fatigue	5 (2)	–
Anorexia	5 (2)	–
Anemia	4 (2)	–
Hyponatremia	1 (<1)	–
Pleural effusion	–	1 (<1)

Cytokine-release-related symptoms

As the release of pro-inflammatory and cytotoxic cytokines is initiated by the binding of Removab® to immune and tumor cells, cytokine-release-related symptoms have been reported during and after Removab® infusions. Very commonly reported grade 1 and 2 symptoms were fever, nausea, vomiting, and chills, which were fully reversible. The incidence of grade 3/4 cytokine-release-related symptoms is shown in Table 12.

Table 12. Incidence of grade 3/4 cytokine-release-related symptoms

Adverse event	Incidence N (%)	
	Grade 3	Grade 4
Pyrexia	13 (5)	0
Vomiting	10 (4)	0
Nausea	6 (2)	0
Dyspnea	4 (2)	1 (<1)
Hypotension	3 (1)	1 (<1)
Chills	2 (1)	0

Symptoms of pain and pyrexia can be ameliorated or avoided by premedication with analgesics, anti-pyretics, or non-steroidal anti-inflammatories.

Systemic Inflammatory Response Syndrome (SIRS)

Systemic inflammatory response syndrome (SIRS) may occur uncommonly due to the mechanism of action of Removab®. It generally develops within 24 hours after Removab® infusion, with symptoms of fever, tachycardia, tachypnea, and leucocytosis. Standard therapy or premedication, e.g. analgesics, anti-pyretics, or non-steroidal anti-inflammatories, can be used to limit the risk.

In 1 % of patients, symptoms of SIRS were observed within 24 hours after Removab® infusion, such as grade 3 tachycardia and fever, and grade 4 dyspnea. These reactions resolved under symptomatic treatment.

Abdominal pain

In 48 % of patients, abdominal pain was reported as an ADR, reaching grade 3 in 10 % of patients, but it resolved under symptomatic treatment.

8. ABBREVIATIONS

ADA	Anti-drug Antibody
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under the Curve (plasma drug concentration time curve)
BMI	Body Mass Index
CEA	CarcinoEmbryonic Antigen
C_{max}	maximum concentration (maximum plasma drug concentration)
CT	Computed Tomography
CTCAE	Common Terminology Criteria of Adverse Events
CUP	Cancer of Unknown Primary
DC	Dendritic Cell
DC-CK	Dendritic Cell CytoKine
DLT	Dose-Limiting Toxicity
EGF	Epidermal Growth Factor
EpCAM	Epithelial Cell Adhesion Molecule
FIGO	International Federation of Gynecology and Obstetrics
GI	GastroIntestinal
GM-CSF	Granulocyte Monocyte Colony Stimulating Factor
HAMA	Human Anti-Mouse Antibody
HARA	Human Anti-Rat Antibody
HR	Hazard Ratio
IFN	InterFeroN
IgG	Immunoglobulin G
IL	InterLeukin
i.p.	intraperitoneal
ITT	Intent To Treat
LFA	Lymphocyte Function Antigen
LLoQ	Lower Limit of Quantification
mAb	monoclonal Antibody
MMP	Matrix MetalloProteinase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NK	Natural Killer
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
SCID	Severe Combined ImmunoDeficiency
SIRS	Systemic Inflammatory Response Syndrome
SPC	Summary of Product Characteristics
TACSTD1	Tumor-Associated Calcium Signal Transducer 1
$t_{1/2}$	half-life
TNF	Tumor Necrosis Factor
trAb	trifunctional Antibody
TTP	Time To Progression
TY	ThYroglobulin
VEGF	Vascular Endothelial Growth Factor

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9
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NEW

Removab®
CATUMAXOMAB

1. NAME OF THE MEDICINAL PRODUCT

Removab® 10 microgram concentrate for solution for infusion

Or

Removab® 50 microgram concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 10 microgram of catumaxomab* in 0.1 ml solution, corresponding to 0.1 mg/ml.

Or

One pre-filled syringe contains 50 microgram of catumaxomab* in 0.5 ml solution, corresponding to 0.1 mg/ml.

* rat mouse hybrid IgG2 monoclonal antibody produced in a rat-mouse hybrid-hybridoma cell line

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Removab® is indicated for the intraperitoneal treatment of malignant ascites in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Removab® must be administered under the supervision of a physician experienced in the use of anti-neoplastic medicinal products.

Adequate monitoring of the patient after end of Removab® infusion is recommended. In the pivotal study patients were monitored for 24 h after each infusion.

Prior to the intraperitoneal infusion pre-medication with analgesic/antipyretic/nonsteroidal antiphlogistic medicinal products is recommended (see section 4.4).

Posology

Removab® dosing schedule comprises the following four intraperitoneal infusions:

1st dose → 10 microgram on day 0

2nd dose → 20 microgram on day 3

3rd dose → 50 microgram on day 7

4th dose → 150 microgram on day 10

An interval of at least two days must elapse between infusions. The interval between the infusion days can be prolonged in case of relevant adverse reactions. The overall treatment period should not exceed 20 days. No dose reductions of Removab® were investigated during clinical trials.

Special populations

• Hepatic impairment

Patients with hepatic impairment of a higher severity grade than moderate and/or with more than 70 % of the liver metastasised and/or portal vein thrombosis/obstruction have not been investigated. Treatment of these patients with Removab® should only be considered after a thorough evaluation of benefit/risk (see section 4.4).

• Renal impairment

Patients with renal impairment of a higher severity grade than mild have not been investigated. Treatment of these patients with Removab® should only be considered after a thorough evaluation of benefit/risk (see section 4.4).

• Paediatric patients

Removab® is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

• Ethnicity

Patients of non-Caucasian origin have not been included in clinical studies.

Method of administration

Removab® must be administered as an **intraperitoneal infusion only.**

Removab® **must not** be administered by intraperitoneal bolus or by any other route of administration.

Before administration of Removab® the concentrate for solution for infusion is diluted in sodium chloride 9 mg/ml (0.9 %) solution for injection. The diluted Removab® solution for infusion is administered intraperitoneally via a constant infusion pump system.

See section 6.6 for detailed instructions on dilution prior to administration and for instructions for administration.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Hypersensitivity to murine (rat and/or mouse) proteins.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Removab® **must not** be administered as a bolus or by any route other than intraperitoneally.

Cytokine release related symptoms

As release of pro-inflammatory and cytotoxic cytokines is initiated by the binding of catumaxomab to immune and tumour cells, cytokine release related clinical symptoms such as fever, nausea, vomiting and chills have been very commonly reported during and after the Removab® administration (see section 4.8). Dyspnoea and hypo-/hypertension are commonly observed. In the clinical studies in patients with malignant ascites, 1000 mg paracetamol intravenously was routinely administered prior to Removab® infusion for pain and pyrexia control. Despite this premedication, patients experienced the adverse reactions described above with an intensity of up to grade 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the US National Cancer Institute. Other or additional standard pre-medication with analgesic/antipyretic/nonsteroidal antiphlogistic medicinal products is recommended.

Systemic Inflammatory Response Syndrome (SIRS), which may also occur uncommonly due to the mechanism of action of catumaxomab, develops, in general, within 24 hours after Removab® infusion, showing symptoms of fever, tachycardia, tachypnoea and leucocytosis (see section 4.8). Standard therapy or premedication, e.g. analgesic/antipyretic/nonsteroidal antiphlogistic is appropriate to limit the risk.

NEW

Removab®
CATUMAXOMAB

Abdominal pain

Abdominal pain was commonly reported as an adverse reaction. This transient effect is considered partially a consequence of study procedures such as the intraperitoneal route of administration.

Performance status and BMI

A solid performance status expressed as Body Mass Index (BMI) > 17 (to be assessed after drainage of ascites fluid) and Karnofsky Index > 60 is required prior to Removab® therapy.

Acute infections

In presence of factors interfering with the immune system, in particular acute infections, the administration of Removab® is not recommended.

Ascites drainage

Appropriate medical management of ascites drainage is a prerequisite for Removab® treatment in order to assure stable circulatory and renal functions. This must at least include ascites drainage until stop of spontaneous flow, and, if appropriate, supportive replacement therapy with crystalloids and/or colloids. Conditions such as hypovolaemia, hypoproteinaemia, hypotension, circulatory decompensation and acute renal impairment should be resolved prior to each Removab® infusion.

Hepatic impairment or portal vein thrombosis/obstruction

Patients with hepatic impairment of a higher severity grade than moderate and/or with more than 70 % of the liver metastasised and/or portal vein thrombosis/obstruction have not been investigated. Treatment of these patients with Removab® should only be considered after a thorough evaluation of benefit/risk.

Renal impairment

Patients with renal impairment of a higher severity grade than mild have not been investigated. Treatment of these patients with Removab® should only be considered after a thorough evaluation of benefit/risk.

Perfusion system

Only the following material must be used for the application of Removab®:

- 50 ml polypropylene syringes
- polyethylene perfusion tubing with an inner diameter of 1 mm and a length of 150 cm
- polycarbonate infusion valves/Y connections
- polyurethane, polyurethane silicon coated catheters

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed.

4.6 PREGNANCY AND LACTATION

There are no adequate data from the use of Removab® in pregnant women. Animal reproduction studies have not been performed with catumaxomab. The potential risk for humans is unknown. Therefore, Removab® should not be used during pregnancy unless clearly necessary.

It is unknown whether catumaxomab is excreted in human breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Removab® therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

4.8 UNDESIRABLE EFFECTS

The nature and frequency of adverse reactions described in this section were analysed in an integrated safety analysis on the basis of 5 clinical studies consisting of 258 patients in the indications malignant ascites (193 patients), peritoneal carcinomatosis (24 patients) and ovarian cancer (41 patients) with intraperitoneal application of Removab®.

Approximately 90 % of patients experienced adverse reactions. In Table 1, adverse reactions reported with catumaxomab are listed and classified according to frequency and System Organ Class. Frequency groupings are defined according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100).Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions with catumaxomab

Blood and lymphatic system disorders	
Very common	Lymphopenia.
Common	Leucocytosis, anaemia, neutrophilia, thrombocythaemia.
Cardiac disorders	
Common	Tachycardia.
Ear and labyrinth disorders	
Common	Vertigo.
Gastrointestinal disorders	
Very common	Abdominal pain*, nausea, vomiting, diarrhoea.
Common	Ileus*, sub-ileus*, constipation, dyspepsia, abdominal distension, flatulence, gastric disorder, gastroesophageal reflux disease, stomatitis.
Uncommon	Gastric haemorrhage*, intestinal obstruction*.
General disorders and administration site conditions	
Very common	Pyrexia*, fatigue, chills, pain.
Common	Asthenia, influenza-like illness, chest pain, oedema, thirst.
Uncommon	Application site inflammation*, extravasation*.
Hepatobiliary disorders	
Common	Hyperbilirubinaemia, cytolytic hepatitis.

Infections and infestations	
Common	Infection, erythaema induratum, urinary tract infection.
Uncommon	Catheter-related infection*, skin infection*.
Metabolism and nutrition disorders	
Common	Anorexia, hyponatraemia, hypocalcaemia, hypokalaemia, hypoproteinaemia, dehydration, hyperglycaemia.
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, back pain, myalgia.
Nervous system disorders	
Common	Headache, dizziness.
Uncommon	Convulsion*.
Psychiatric disorders	
Common	Anxiety, insomnia.
Renal and urinary disorders	
Common	Oliguria, leucocyturia, proteinuria, haematuria.
Uncommon	Renal failure acute*.
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea*, pleural effusion.
Uncommon	Pulmonary embolism*, pleural effusion*.
Skin and subcutaneous tissue disorders	
Common	Exanthema, dermatitis allergic, skin reaction, erythaema, rash, hyperhidrosis, pruritus, urticaria.
Uncommon	Dermatitis allergic*, rash*, skin exfoliation*, skin reaction*.
Vascular disorders	
Common	Hypotension, hypertension, flushing, hot flush.

* were also reported as serious adverse reactions

Adverse reactions of special interest

The following definitions of CTCAE criteria of the US National Cancer Institute apply: CTCAE grade 1 = mild, CTCAE grade 2 = moderate, CTCAE grade 3 = severe, CTCAE grade 4 = life-threatening

• *Cytokine release related symptoms:*

Very commonly reported acute infusion-related reactions due to release of cytokines included fever, nausea, vomiting and chills. These reactions were frequently observed during and after Removab® infusions with a severity of grade 1 and 2 and were fully reversible. Grade 3 pyrexia (5%), vomiting (3.9%), nausea (2.3%), dyspnoea (1.6%) hypotension (1.2%), hypertension (0.8%) and chills (0.8%) were reported. Grade 4 dyspnoea and hypotension were also reported in one patient each. Symptoms of pain and pyrexia can be ameliorated or avoided by pre-medication (see sections 4.2 and 4.4).

• *Systemic Inflammatory Response Syndrome (SIRS):*

In 0.8 % of the patients symptoms of SIRS were observed within 24 hours after Removab® infusion, such as grade 3 tachycardia and fever and grade 4 dyspnoea. These reactions resolved under symptomatic treatment.

• *Abdominal pain:*

In 48.1% of patients abdominal pain was reported as an adverse reaction reaching grade 3 in 9.7 % of patients, but it resolved under symptomatic treatment.

4.9 OVERDOSE

No case of overdose has been reported. Patients receiving a higher than recommended dose of catumaxomab experienced more severe (grade 3) adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other antineoplastic agents, Monoclonal antibodies, ATC code: L01XC09

Mechanism of action

Catumaxomab is a trifunctional rat-mouse hybrid monoclonal antibody that is specifically directed against the epithelial cell adhesion molecule (EpCAM) and the CD3 antigen.

The EpCAM antigen is overexpressed on most carcinomas. CD3 is expressed on mature T-cells as a component of the T-cell receptor. A third functional binding site in the Fc-region of catumaxomab enables interaction with accessory immune cells via Fcγ receptors.

Due to catumaxomab's binding properties, tumour cells, T-cells and accessory immune cells come in close proximity. Thereby, a concerted immunoreaction against tumour cells is induced which includes different mechanisms of action such as T-cell activation, antibody-dependent cell mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and phagocytosis. This results in destruction of tumour cells.

Pharmacodynamic effects

The anti-tumour activity of catumaxomab has been demonstrated *in vitro* and *in vivo*. Effective catumaxomab-mediated killing of tumour cells *in vitro* was observed for target cells with low and high expression of the EpCAM antigen, independent of the primary tumour type. The *in vivo* anti-tumour activity of catumaxomab was confirmed in an immunologically compromised mouse model of ovarian carcinoma, where tumour development was delayed by an intraperitoneal treatment with catumaxomab and human peripheral blood mononuclear cells.

NEW

Removab® CATUMAXOMAB

Clinical efficacy

The efficacy of catumaxomab was demonstrated in a two-arm, randomised, open-label clinical trial (IP-REM-AC-01) in 258 patients with symptomatic malignant ascites due to EpCAM-positive carcinomas of whom 170 were randomised to catumaxomab treatment. This study compared paracentesis plus catumaxomab *versus* paracentesis alone (control).

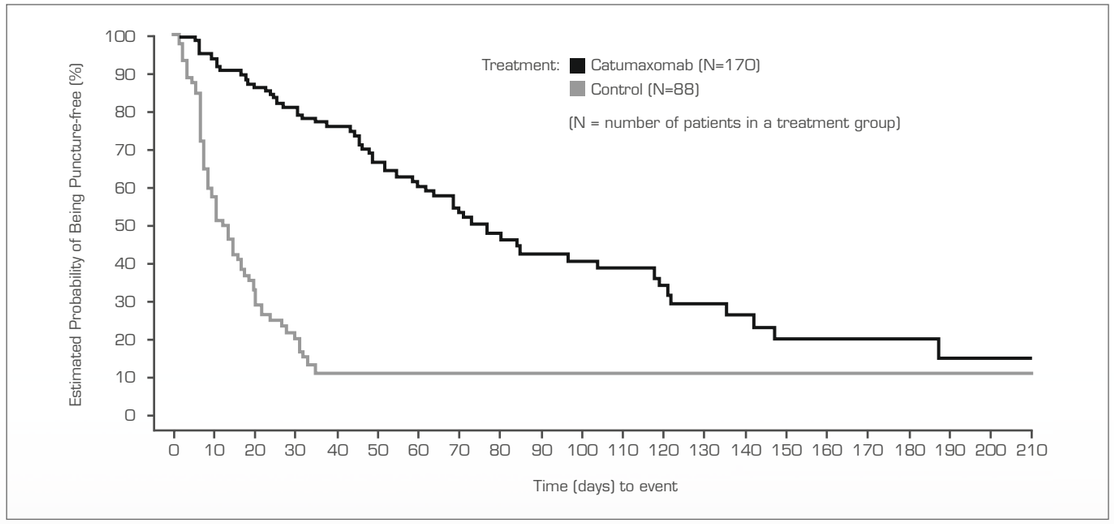
Catumaxomab was applied in patients where standard therapy was not available or no longer feasible and who had a Karnofsky performance status of a least 60. Catumaxomab was administered as four intraperitoneal infusions with increased doses of 10, 20, 50 and 150 micrograms on day 0, 3, 7 and 10, respectively (see section 4.2). In the pivotal study IP-REM-AC-01 98.1 % of patients were hospitalised for a median of 11 days.

In this study, the primary efficacy endpoint was puncture-free survival, which was a composite endpoint defined as the time to first need for therapeutic ascites puncture or death, whichever occurred first. The results for puncture-free survival and time to first need for therapeutic ascites puncture in terms of medians and hazard ratios are presented in Table 2. Kaplan Meier estimates for time to first need for therapeutic ascites puncture are given in Figure 1.

Table 2: Efficacy results (puncture free survival and time to first need for therapeutic ascites puncture) of study IP-REM-AC-01 [95 % CI]

Variable	Paracentesis + catumaxomab (N=170)	Paracentesis (control) (N=88)
Puncture free survival		
Median puncture-free survival (days)	44	11
95 % CI for median (days)	[31; 49]	[9; 16]
p-value (log-rank test)	< 0.0001	
Hazard ratio (HR)	0.310	
95 % CI for HR	[0.228; 0.423]	
Time to first need for therapeutic ascites puncture		
Median time to first need for therapeutic ascites puncture (days)	77	13
95 % CI for median (days)	[62; 104]	[9; 17]
p-value (log-rank test)	< 0.0001	
Hazard ratio (HR)	0.169	
95 % CI for HR	[0.114; 0.251]	

Figure 1: Kaplan-Meier estimates of time to first need for therapeutic ascites puncture of study IP-REM-AC-01



The efficacy of the treatment with paracentesis and catumaxomab in patients with malignant ascites due to EpCAM-positive carcinomas was statistically significantly superior to that with paracentesis alone in terms of puncture-free survival and time to first need for therapeutic ascites puncture.

After completion of the study, patients were further observed until the end of their lifetime (post-study phase) in order to assess overall survival (Table 3).

Table 3: Overall survival of study IP-REM-AC-01 in post study phase [95 % CI]

	Paracentesis + catumaxomab (N=170)	Paracentesis (control) (N=88)
Overall survival (days)	72	68
95 % CI for median (days)	[61; 98]	[49; 81]
p-value (log-rank test)	0.0846	
Hazard ratio (HR)	0.723	
95 % CI for HR	[0.498; 1.048]	

A positive trend for median overall survival after treatment with catumaxomab compared to control was seen.

Immunogenicity

The induction of human anti-murine (rat and/or mouse) antibodies (HAMAs/HARAs) is an intrinsic effect of murine monoclonal antibodies. Current data on catumaxomab derived from the pivotal study show that only 5 % of patients (7/132 patients) were HAMA positive before the 4th infusion. HAMAs were present in 87 % of patients one month after the last catumaxomab infusion. No data about clinical effects due to the presence of HAMAs/HARAs are available to date. No hypersensitivity reactions were observed.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics of catumaxomab during and after four intraperitoneal infusions of 10, 20, 50 and 150 microgram catumaxomab were investigated in 13 patients with symptomatic malignant ascites due to EpCAM-positive carcinomas.

The variability between subjects was high. The geometric mean plasma C_{max} was approximately 0.5 ng/ml (range 0 to 2.3), and the geometric mean plasma AUC was approximately 1.7 day* ng/ml (range < LLOQ (lower limit of quantification) to 13.5). The geometric mean apparent terminal plasma elimination half-life ($t_{1/2}$) was approximately 2.5 days (range 0.7 to 17).

Catumaxomab was detectable in the ascites fluid and in plasma. The concentrations increased with the number of infusions and the doses applied in most patients. Plasma levels tended to decline after achieving a maximum after each dose

Special populations

No studies have been conducted.

5.3 PRECLINICAL SAFETY DATA

Administration of catumaxomab in animal models did not result in any signs of abnormal or drug-related acute toxicity or signs of local intolerance at the injection/infusion site. However, these findings are of limited value due to the high species-specificity of catumaxomab.

Repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium citrate
Citric acid monohydrate
Polysorbate 80
Water for injections

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 SHELF LIFE

24 months

After dilution

The prepared solution for infusion is physically and chemically stable for 48 hours at 2°C to 8°C and for 24 hours at a temperature not above 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C–8°C). Do not freeze. Store in the original package in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

0.1 ml concentrate for solution for infusion in a pre-filled syringe (type I glass, siliconised) with plunger stopper (bromobutyl rubber) and luer lock system (polypropylene siliconised and polycarbonate) with tip cap (styrene butadiene rubber) with a cannula; pack size of 1.

Or

0.5 ml concentrate for solution for infusion in a pre-filled syringe (type I glass, siliconised) with plunger stopper (bromobutyl rubber) and luer lock system (polypropylene siliconised and polycarbonate) with tip cap (styrene butadiene rubber) with a cannula; pack size of 1.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Disposal

No special requirements.

Material and equipment required

The following components must be used for the dilution and administration of Removab® as Removab® is only compatible with:

- 50 ml polypropylene syringes
- polyethylene perfusion tubings with an inner diameter of 1 mm and a length of 150 cm
- polycarbonate infusion valves/Y connections
- polyurethane, polyurethane silicon coated catheters

In addition the following is required:

- Sodium chloride 9 mg/ml (0.9 %) solution for injection
- Precision perfusion pump

NEW

Removab® CATUMAXOMAB

Instructions for dilution prior to administration

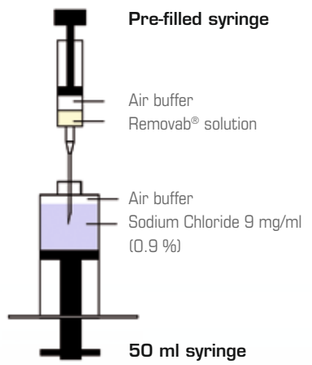
Removab® should be prepared by a healthcare professional using appropriate aseptic technique. The outer surface of the pre-filled syringe is not sterile.

- Based on the dose, the appropriate amount of sodium chloride 9 mg/ml (0.9 %) solution for injection is extracted with a 50 ml syringe (Table 4).
- An additional air buffer of at least 3 ml is included in the 50 ml syringe.
- The tip cap from the Removab® pre-filled syringe is removed with the tip pointing up.
- The enclosed cannula is attached to the Removab® pre-filled syringe. For each syringe a new cannula is used.
- The pre-filled syringe cannula is inserted through the 50 ml syringe opening so that the cannula is immersed in the sodium chloride 9 mg/ml (0.9 %) solution for injection (Figure 2).
- The entire content of the syringe (Removab® concentrate plus air buffer) is injected from the pre-filled syringe directly into the sodium chloride 9 mg/ml (0.9 %) solution for injection.
- The plunger rod MUST NOT be drawn back to rinse the pre-filled syringe, in order to avoid contamination and to ensure that the correct volume is ejected.
- The 50 ml syringe is closed with a cap and shaken gently to mix the solution. Any air bubble(s) from the 50 ml syringe is eliminated.
- The 50 ml syringe is inserted in the infusion pump.

Table 4: Preparation of Removab® solution for intraperitoneal infusion

Number of infusion/Dose		Number of Removab® pre-filled syringe(s)		Total volume of Removab® concentrate for solution for infusion	Sodium chloride 9 mg/ml (0.9 %) solution for injection	Final volume for administration
		10 microgram pre-filled syringe	50 microgram pre-filled syringe			
1st infusion	10 µg	1		0.1 ml	10 ml	10.1 ml
2nd infusion	20 µg	2		0.2 ml	20 ml	20.2 ml
3rd infusion	50 µg		1	0.5 ml	49.5 ml	50 ml
4th infusion	150 µg		3	1.5 ml	48.5 ml	50 ml

Figure 2: Illustration of the transfer of Removab® from the pre-filled syringe to the 50 ml syringe



Method of administration

The catheter for intraperitoneal administration should be placed under ultrasound guidance by a physician experienced in intraperitoneal administration procedures. The catheter is used for ascites drainage and infusion of diluted Removab® and sodium chloride 9 mg/ml (0.9 %) solution for injection. It is recommended that the catheter remains in the abdominal cavity during the entire treatment period. It can be removed the day after the last infusion.

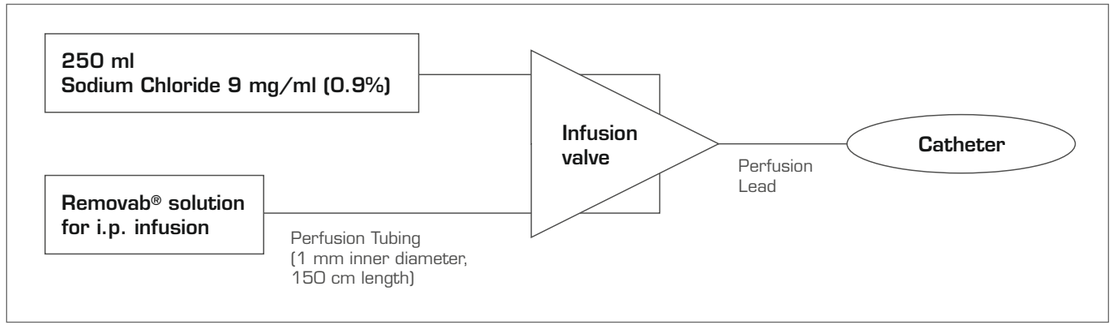
Prior to each Removab® administration the ascites fluid must be drained until stop of spontaneous flow (see section 4.4). Subsequently, prior to each Removab® administration 500 ml sodium chloride 9 mg/ml (0.9%) solution for injection shall be infused to support distribution of the antibody in the abdominal cavity.

Removab® must be administered intraperitoneally over 6 hours via a constant infusion pump system as described below:

- The 50 ml syringe containing the diluted Removab® solution for infusion is installed in the precision pump.
- The connected perfusion tubing equipment of the precision pump is prefilled with the diluted Removab® solution for infusion. A perfusion tubing of an inner diameter of 1 mm and a length of 150 cm must be used.

- The perfusion tubing is connected to the Y-connection.
- Parallel to each Removab® application 250 ml sodium chloride 9 mg/ml (0.9 %) solution for injection are infused via an infusion valve/Y connection in the perfusion lead of the catheter.
- The pump speed is adjusted according to the volume to be administered and the infusion time of 6 hours.
- After completion of the Removab® infusion 20 ml sodium chloride 9 mg/ml (0.9 %) solution for injection are infused briefly to clear the dead volume in the perfusion lead.
- The catheter is kept closed until the next infusion.
- The day after the last infusion a drainage of ascites until stop of spontaneous flow is performed. Subsequently, the catheter can be removed.

Figure 3: Schematic illustration of the infusion system



7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/512/001
EU/1/09/512/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/04/2009

10. DATE OF REVISION OF THE TEXT

12/2009

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.ema.europa.eu/

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NOTES

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TRION PHARMA

FRESENIUS BIOTECH

Catumaxomab is a trifunctional antibody licensed from TRION Pharma GmbH*.
Trifunctional antibodies are a development of TRION Pharma GmbH, Germany.
*Patents: EP 1315520, EP 0826696, EP 0763128