Review

Novel Monoclonal Antibodies for Cancer Treatment: The Trifunctional Antibody Catumaxomab (Removab®)

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Abstract

The trifunctional antibody (trAb) catumaxomab is characterized by a unique ability to bind three different cell types: tumor cells; T-cells; and accessory cells. It binds to epithelial cell adhesion molecule (EpCAM) on tumor cells, the CD3 antigen on T-cells, and to type I, IIa, and III Fcγ receptors (FcγRs) on accessory cells (e.g. natural killer cells, dendritic cells, and macrophages). Catumaxomab exerts its anti-tumor effects via T-cell-mediated lysis, antibody-dependent, cell-mediated cytotoxicity, and phagocytosis via activation of FcγR-positive accessory cells. Catumaxomab represents a self-supporting system, as no additional immune cell activation is required for tumor eradication. The efficacy and safety of catumaxomab have been demonstrated in a pivotal phase II/III study in malignant ascites (MA) and supporting phase I/II studies. It is administered as four intraperitoneal (i.p.) infusions of 10, 20, 50, and 150 µg on days 0, 3, 7, and 10, respectively. Catumaxomab was approved for the i.p. treatment of MA in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible in the European Union in April 2009. It is the first trAb and the first drug in the world approved specifically for the treatment of MA. Catumaxomab was awarded the Galen of Pergamon Prize, which recognizes pharmacological research for developing new and innovative drugs and diagnostics, in the specialist care category in 2010. The use of catumaxomab in other indications and additional routes of administration are currently being investigated to further exploit its therapeutic potential in EpCAM-positive carcinomas.

Key words: catumaxomab, epithelial cell adhesion molecule (EpCAM), anti-EpCAM × anti-CD3, trifunctional antibody; targeted cancer immunotherapy, malignant ascites

Introduction

The development of monoclonal antibodies (mAbs), which act via antibody-dependent cell-mediated cytotoxicity (ADCC), represented a significant advance in cancer immunotherapy.[1] Bispecific antibodies (bsAbs), which bind to tumor cells and T-cells, and act via T-cell-mediated lysis, are currently in clinical development.[2,3] The trifunctional antibody (trAb) catumaxomab (Removab®, Fresenius Biotech GmbH, Munich, Germany) is characterized by a unique ability to bind three different cell types: tumor cells, T-cells, and accessory cells.[4-6] It was approved in the European Union (EU) in April 2009 for the intraperitoneal (i.p.) treatment of malignant ascites (MA) in patients with epithelial cell adhesion molecule (EpCAM)-positive carcinomas where standard therapy is not available or no longer feasible.

Catumaxomab is the first trAb and the first drug in the world approved specifically for the treatment of MA.

Catumaxomab

Catumaxomab has two different antigen-binding specificities: one for EpCAM on tumor cells and one for the CD3 antigen on T-cells. In addition, catumaxomab binds, via its intact Fc region, to type I, IIa, and III Fcγ receptors (FcγRs) on accessory cells, e.g. natural killer (NK) cells, dendritic cells (DCs), and macrophages. Catumaxomab exerts its anti-tumor effects via T-cell-mediated lysis,[7] ADCC, and phagocytosis via activation of FcγR-positive accessory cells (Figure 1).[5,6] Its anti-tumor activity is assisted by the induction of T-cell-secreted cytokines, such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α.[8] An important aspect of catumaxomab's mode of action is that no additional activation of immune cells is required for effective tumor eradication, so it is a self-supporting system.

Malignant Ascites

MA is an increased accumulation of protein-containing fluid within the peritoneal cavity that is caused by i.p. spread of cancer. It is associated with advanced ovarian cancer, gastrointestinal malignancies, and other carcinomas, and leads to abdominal pain and swelling, dyspnea, nausea, vomiting, malnutrition, and anorexia.[9,10] Patients with MA have a poor quality of life,[9,11] and a poor prognosis, with median overall survival (OS) of approximately 1–6 months.[9,12,13] The causes of MA are independent of the origin of the primary tumor (Figure 2).[14-17] Tumor-secreted factors lead to tumor neovascularization and increased capillary permeability, resulting in increased plasma inflow into the peritoneal cavity. Tumor cells obstruct lymphatic drainage, leading to decreased fluid efflux from the peritoneal cavity.

Rationale for use of Catumaxomab in the Treatment of MA

Prior to the approval of catumaxomab, no agents were specifically approved for the treatment of MA and treatment options, such as peritoneovenous shunts, paracentesis, and diuretics, are only palliative.[11] There was thus a need for an effective treatment for MA. The rationale for the use of catumaxomab for the i.p. treatment of MA was four-fold: 1) epithelial tumors spreading into the peritoneal cavity play a major role in the development of MA; 2) epithelial tumors frequently express EpCAM;[18-21] 3) in the peritoneal cavity, EpCAM is a tumor-specific antigen; and 4) immune effector cells are present in MA.[22,23] Targeting EpCAM by i.p. administration of catumaxomab leads to a depletion of epithelial tumor cells in the peritoneal cavity and a sustained reduction of MA production.
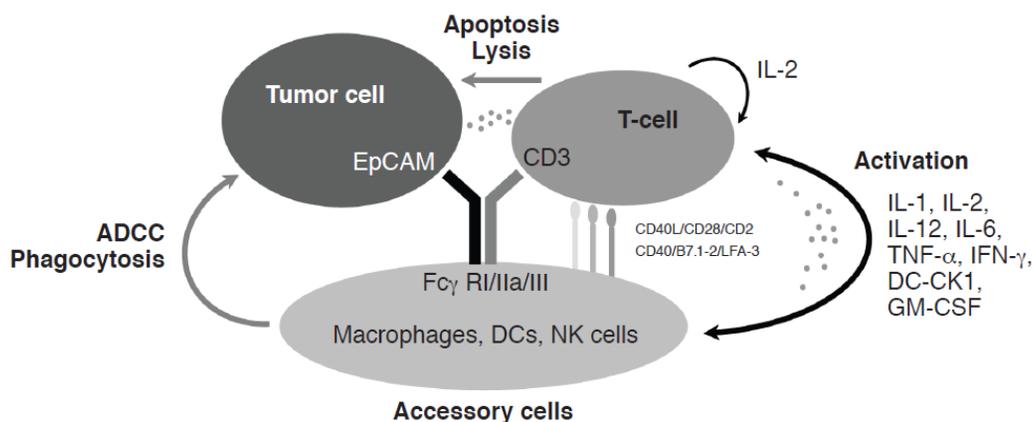
Figure 1. Catumaxomab mechanism of action. ADCC = antibody-dependent cell-mediated cytotoxicity, CK = cytokine, DC = dendritic cell, EpCAM = epithelial cell adhesion molecule, Fcγ R = Fcγ receptor, GM-CSF = granulocyte-macrophage colony-stimulating factor, IL = interleukin, IFN = interferon, LFA = lymphocyte function-associated antigen, NK = natural killer, TNF = tumor necrosis factor.
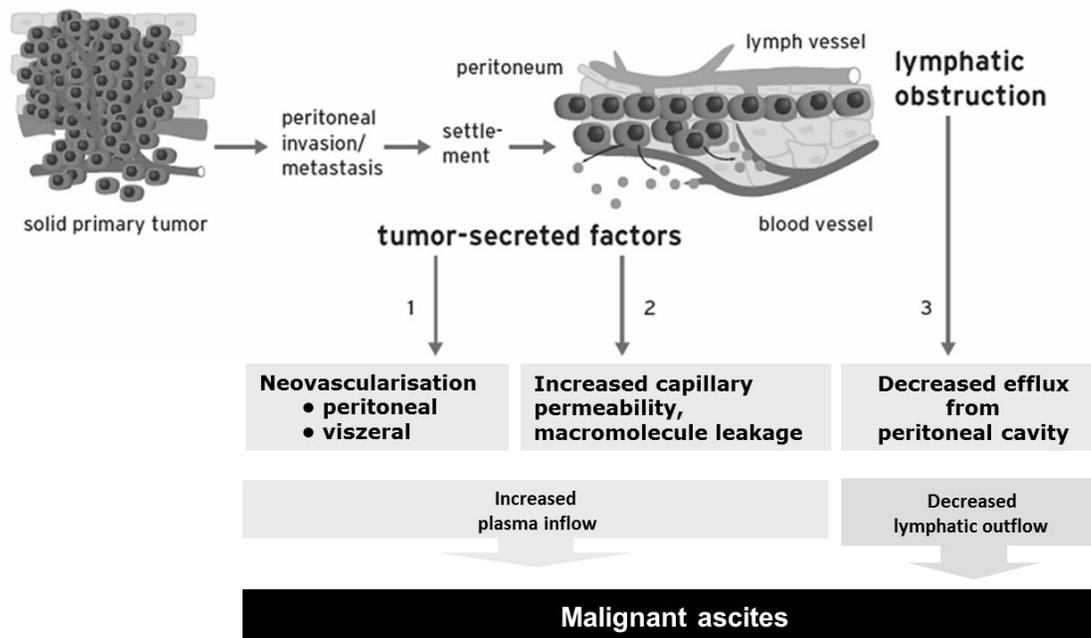
Figure 2. Pathophysiology of malignant ascites.

Table 1. Clinical development of catumaxomab in malignant ascites.

Study number	Indication (No. of treated patients)	Phase	Study design	Key results
STP-REM-01[24]	Malignant ascites due to ovarian cancer (23)	I/II	Multicenter, multinational, open label, uncontrolled, sequential dose escalation	Recommended dose 10, 20, 50, 150 µg Efficacy: Reduction of ascites flow; no requirement for puncture in 22 patients at study end
IP-REM-PK-01-EU	Malignant ascites due to epithelial cancer (13)	II	Multicenter, open label, pharmacokinetic	i.p. catumaxomab measurable in plasma $t_{1/2}$: geometric mean ~2 days High inter-subject variability
IP-REM-AC-01[25]	Malignant ascites due to epithelial cancer (157)	II/III	Multicenter, multinational, two arm, randomized, open label	Statistically significant and clinically relevant superiority of catumaxomab plus paracentesis versus paracentesis alone

Clinical Development of Catumaxomab in MA

The clinical development of catumaxomab in MA consisted of three key studies: an open-label phase I/II dose-finding study (STP-REM-01);[24] a pharmacokinetic study (IP-REM-PK-01-EU); and a pivotal phase II/III study (IP-REM-AC-01)[25] (Table 1). A phase II and two phase I studies in other indications (ovarian cancer [AGO-OVAR-2.10],[26] peritoneal carcinomatosis [IP-REM-PC-01-DE],[27] and intra-abdominal epithelial cancers [IP-REM-GC-01]),[28] provided supporting efficacy and safety data. In total, 270 patients received catumaxomab in these studies.

STP-REM-01

This study investigated the maximum tolerated dose (MTD) of catumaxomab in 23 women with re-current ascites due to treatment-refractory ovarian cancer.[24] Patients received four or five 6-hour i.p. catumaxomab infusions 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. Catumaxomab produced a significant and sustained reduction in ascites flow rate, and 22 patients did not require paracentesis between the last infusion and end of the study (day 37). EpCAM-positive tumor cells in ascites were reduced by up to 5 logs and were eliminated to levels below the limit of detection. The MTD was determined to be 10, 20, 50, 200, and 200 µg.

Most adverse events were reversible and resolved without sequelae. Frequent adverse events were transient fever (83%), nausea (61%), and vomiting (57%), which were mostly grade 1/2. Although there was no clear relationship between catumaxomab dose and the severity of adverse events, which

is similar to other cancer immunotherapies,[29] a dose schedule of 10, 20, 50, and 150 µg that is well below the MTD was recommended for further studies.

IP-REM-PK-01-EU

This was an open-label, multicenter, pharmacokinetic study in 13 patients who received four i.p. catumaxomab infusions of 10, 20, 50, and 150 µg. In most patients, the catumaxomab concentration increased with the number of infusions and the doses applied. The highest concentrations of catumaxomab were found in ascitic fluid, the site of intended efficacy. Catumaxomab could be detected in plasma after the third and fourth i.p. infusions, demonstrating systemic availability. Inter-patient variability was high. The geometric mean maximum plasma drug concentration (C_{max}) was approximately 0.5 ng/mL and the mean terminal plasma elimination half-life ($t_{1/2}$) was approximately 2.5 days.[30]

IP-REM-AC-01

This pivotal phase II/III, multicenter study was a two-arm, randomized (2:1), open-label design that compared catumaxomab plus paracentesis with paracentesis alone (control) in 258 patients stratified by cancer type (ovarian or nonovarian; n=129: 85 catumaxomab/44 control in each group).[25] Catumaxomab was administered as four 6-hour i.p. infusions of 10, 20, 50, and 150 µg on days 0, 3, 7, and 10, respectively. Puncture-free survival, defined as the time after day 0 (control group)/1 day after last infusion (catumaxomab group) to the first need for therapeutic paracentesis or death, whichever occurred first, was the primary endpoint. Secondary endpoints included time to next therapeutic paracentesis, ascites signs and symptoms, OS, and safety. The main inclusion criteria were resistance to chemotherapy or chemotherapy no longer feasible, at least one previous puncture within 5 weeks before screening, symptomatic ascites with a volume of >1 L, EpCAM-positive tumor cells in the ascites, and a Karnofsky Index ≥60.

Catumaxomab significantly prolonged puncture-free survival versus paracentesis alone in the intent-to-treat (ITT) population, in the pooled (Figure 3), ovarian, and nonovarian cancer populations (all p<0.0001). The median difference was 35 (95% CI: 25–45), 41 (95% CI: 32–50), and 23 (95% CI: 8–38) days in the pooled, ovarian, and nonovarian cancer populations, respectively. The hazard ratio (HR) for the pooled population corresponded to a risk reduction of 75% for puncture or death. Catumaxomab also significantly prolonged the median time to next therapeutic paracentesis versus paracentesis alone: 77 versus 13, 71 versus 11, and 80 versus 15 days in the

pooled, ovarian, and nonovarian cancer populations, respectively (all p<0.0001). This corresponds to a saving of about five punctures for catumaxomab, which is clinically relevant as there is continuous protein loss with each puncture that leads to cachexia and a potential risk of infection and bowel perforation.

Ascites signs and symptoms were analyzed 8 days after the last catumaxomab infusion or after day 0 in the control group.[25] Catumaxomab significantly (p<0.05) improved ascites-related symptoms in six of 10 categories (abdominal pain, nausea, abdominal swelling, dyspnea, anorexia, and early satiety) (Figure 4) and in all four sign categories (abdominal distension dull to percussion, shifting dullness, fluid thrill, and bulging flanks). There was a trend towards prolonged OS with catumaxomab, although the study was not powered or designed to detect statistically significant differences in OS. Median OS was 72 versus 68, 110 versus 81, and 52 versus 49 days in the pooled, ovarian, and nonovarian cancer populations, respectively. In the subgroup of patients with gastric cancer, there was a statistically significant difference between catumaxomab and paracentesis alone (71 versus 44 days, p=0.0313).[25] A long-term survival analysis showed that the 6- and 12-month survival rates for catumaxomab plus paracentesis versus paracentesis alone in the ITT population were 27.5% versus 6.7% and 11.4% versus 3.4%, respectively.[31]

Catumaxomab had an acceptable safety profile: most adverse events were generally mild to moderate and fully reversible. The majority of patients (n=131; 83%) received all four i.p. infusions. The most common drug-related adverse events were cytokine-release-related symptoms (CRRSs), i.e. pyrexia, nausea, and vomiting, and abdominal pain. These symptoms are due to catumaxomab's mechanism of action and are well-known side effects of antibody therapy.[32,33] Transient increases in liver parameters and white blood cell abnormalities occurred but were rarely considered to be clinically significant. There was no distinctive pattern of adverse events corresponding to specific infusions.

The results of this study demonstrated that catumaxomab, administered as a sequence of four i.p. infusions of 10, 20, 50, and 150 µg, had a positive risk-benefit profile. Catumaxomab plus paracentesis resulted in significant prolongation of puncture-free survival and puncture-free time, pronounced reduction of ascites-related symptoms, and improvement in OS. The safety profile of catumaxomab is defined by its mechanism of action and the i.p. route of administration. Adverse events are predictable, limited, reversible, and manageable.
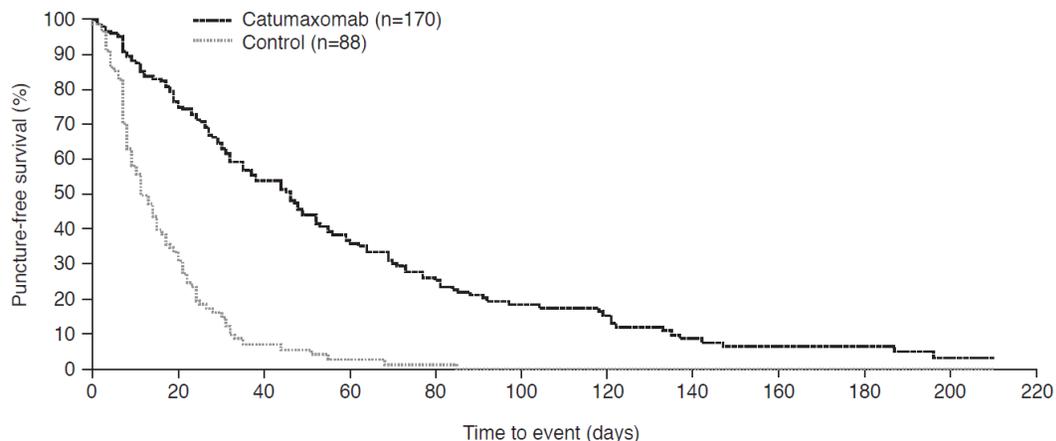
Figure 3. Puncture-free survival in the pooled intent-to-treat population in the pivotal phase II/III study.[25]
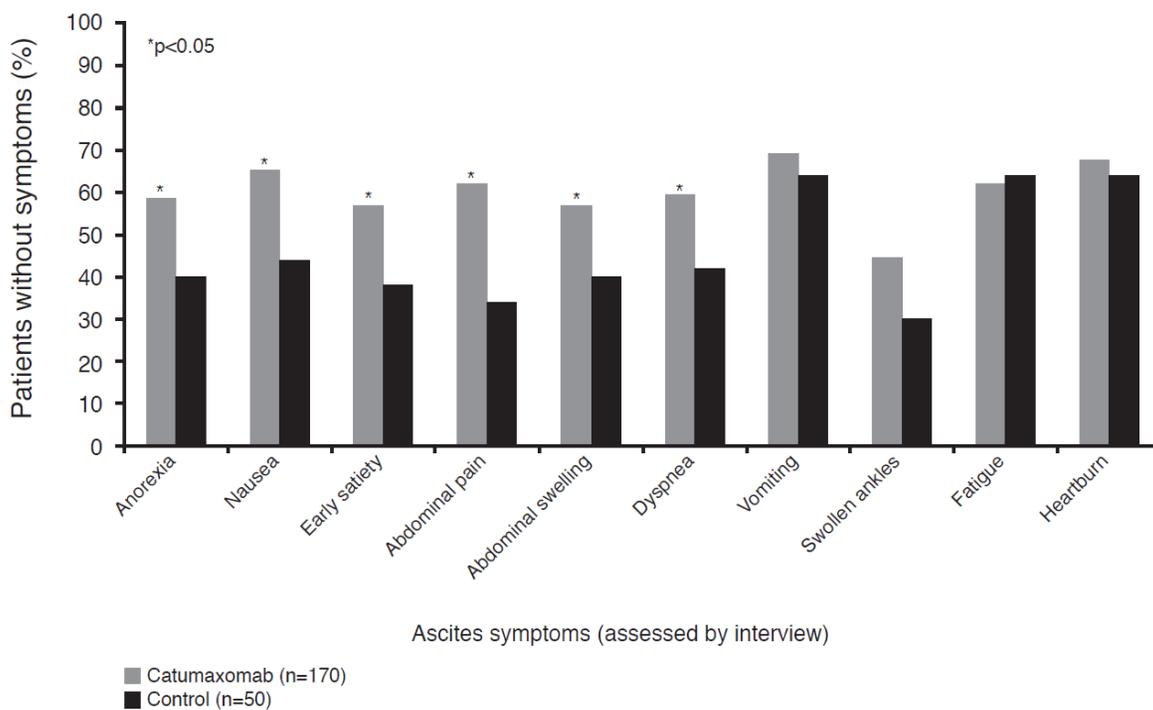
Figure 4. Ascites-related symptoms in the pivotal phase II/III study.[25]
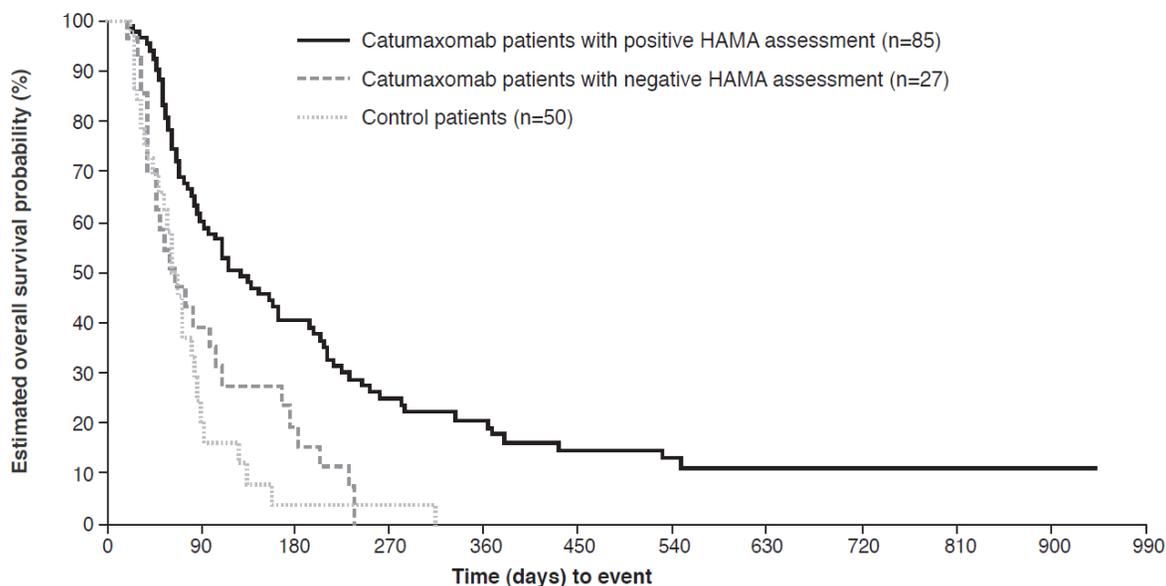
Figure 5. Overall survival in HAMA-positive versus HAMA-negative patients* in the pooled population in the pivotal phase II/III study.[37] *Assessed 8 days after last catumaxomab infusion.

Immunological Response to Catumaxomab

Although the induction of human anti-murine antibodies (human anti-mouse antibodies [HAMAs] and human anti-rat antibodies [HARAs]) is an intrinsic effect of murine mAbs, the available evidence indicates that they are not associated with any major safety issues.[34,35] In fact, the development of HAMAs/HARAs can be associated with beneficial immunity and prolonged survival.[34,36] A post-hoc analysis of the pivotal phase II/III trial demonstrated that there was a strong correlation between clinical outcome and humoral response, as measured by the detection of HAMAs 8 days after the fourth catumaxomab infusion.[37] HAMA-positive and HAMA-negative catumaxomab-treated patients and control patients were analyzed separately for puncture-free survival, time to next puncture, and OS, and compared with each other. In the pooled population, patients who developed HAMAs after catumaxomab treatment showed significant improvement in all three clinical outcome measures compared with HAMA-negative patients: median puncture-free survival was 64 versus 27 days (p<0.0001; HR 0.330), median time to next therapeutic puncture was 104 versus 46 days (p=0.0002; HR 0.307), and median OS was 129 versus 64 days (p=0.0003; HR 0.433) (Figure 5). Similar differences were seen in the ovarian, nonovarian, and gastric cancer populations. The results showed that HAMA development may be a biomarker for catumaxomab response and patients who developed HAMAs sooner derived greater benefit from catumaxomab therapy.

EU Approval Procedure

Catumaxomab was developed and approved in the EU for the treatment of MA within 8 years. The dose-finding study commenced in November 2001, the pivotal study started in 2004 and reported in 2007, and the pharmacokinetic study plus three supporting studies were conducted between 2003 and 2007. The Committee for Human Medicinal Products (CHMP) provided scientific advice, particularly for the design of the pivotal study, including the selection of a suitable endpoint for MA, as no standards were available at the time of catumaxomab's clinical development. The most appropriate endpoint to show potential treatment benefits, taking into account the terminal nature of the disease, was identified as puncture-free survival, a combined endpoint of time to puncture or death, whichever occurs first.

A Marketing Authorization was compiled and submitted in December 2007 after successful completion of the pivotal study. CHMP review, which started in January 2008, included an assessment of the clinical data by the Scientific Advisory Group on Oncology. The CHMP reached a consensus decision that the risk-benefit profile of catumaxomab is positive and recommended authorization in February 2009. The European Commission followed the recommendation of the CHMP and approved catumaxomab (Removab®) in April 2009 for the i.p. treatment of MA in pa-

tients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

The approval of catumaxomab was unique for several reasons: it is the first drug approved specifically for the treatment of MA; to date, it is the only approved EpCAM-targeted antibody; it is the only approved agent based on the target antigen that is independent of the primary tumor type; and it is the first approved trAb.

Catumaxomab was awarded the Galen of Pergamon Prize, which recognizes pharmacological research for developing new and innovative drugs and diagnostics, in the specialist care category in 2010. The prize, which is awarded annually by Springer Medicine to honor excellence in pharmacological research in Germany, was founded in France in 1970.

Further Investigations in Malignant Ascites

Catumaxomab is being investigated in a number of clinical studies. CASIMAS (CAtumaxomab Study with Intraperitoneal infusion in Malignant AScites patients) is a randomized, phase lllb study of a 3-hour infusion of catumaxomab with corticosteroid premedication in an office-based setting. The study is intended to further optimize the administration of catumaxomab by reducing the infusion time from 6 to 3 hours. Repeated catumaxomab treatment cycles are being investigated in the SECIMAS (SEcond Cycle catumaxomab Intraperitoneal infusion Malignant Ascites Safety) study, a follow-on phase ll study to CASIMAS. Patients needing their first therapeutic puncture after treatment in CASIMAS are eligible for enrollment in SECIMAS to receive a second i.p. cycle of catumaxomab 10, 20, 50, and 150 μg. A non-interventional study (CARMA) is documenting treatment behavior.

Further Development Strategy for Catumaxomab

Intravenous infusion is being investigated as an additional route for administration in a phase I study that started at the beginning of 2011. Other indications under investigation for i.p catumaxomab include, for example, peritoneal carcinomatosis in gastric cancer. All carcinomas that express EpCAM could be future targets for catumaxomab therapy.

Conclusions

Catumaxomab's trifunctional mechanism of action utilizes the close proximity and local activation of T-cells and accessory cells against tumor cells. Its efficacy is dependent on the presence of immune effector cells, which confirms the importance of local immunostimulatory effects (e.g. cytokine release and physiological T-cell activation and proliferation) and their contribution to anti-tumor activity. Importantly, no additional activation of immune cells is necessary for effective tumor eradication by catumaxomab, which is thus a self-supporting system. The efficacy and safety of catumaxomab have been demonstrated in a pivotal phase II/III study and supporting phase I/II studies. It is administered as four intraperitoneal (i.p.) infusions of 10, 20, 50, and 150 μg on days 0, 3, 7, and 10, respectively. Treatment with catumaxomab significantly prolongs puncture-free survival, saves approximately five therapeutic punctures, and improves ascites-related symptoms, with a trend towards prolonging OS. Catumaxomab, which was approved in the EU in April 2009, is the first trAb to receive regulatory approval and the first drug in the world approved specifically for the treatment of MA. In 2010, catumaxomab was awarded the Galen von Pergamon Prize, which recognizes pharmacological research for developing new and innovative drugs and diagnostics, in the specialist care category. Clinical development is ongoing in a number of indications including MA and peritoneal carcinomatosis. Shorter administration times, additional routes of administration, and multiple dosing are under evaluation to fully utilize the therapeutic potential of catumaxomab in EpCAM-positive carcinomas.

Acknowledgement

Conflict of Interest

Diane Seimetz is the Chief Scientific Officer and Executive Vice President of Fresenius Biotech GmbH.

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