SYNOPSIS

Name of Sponsor/Company: AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Removab	Volume: NA	
Name of Active Ingredient: Catumaxomab	Page: NA	

Title of Study:

AIO-STO-0110 - Explorative trial to investigate catumaxomab (anti-EpCAM x anti-CD3) for treatment of peritoneal carcinomatosis in patients with gastric adenocarcinomas prior to gastrectomy
EudraCT Nr.: 2010-024111-13

Amendment 1, approved 25.03.2013: Update of the IB, updated patient information, relocation of the "LKP", change of the leading ethics committee, change of sponsors' address.

Amendment 2, approved 18.12.2013: Compulsory participation in the translational program. Expansion of this accompanying program for examinations on the EpCAM protein. The patient information and consent document has been adapted with regard to these modifications.

Amendment 3, approved 22.07.2014: Conversion of all trial sites to "Prüfgruppe" according to 16th "AMG-Novelle".

Amendment 4, approved 09.07.2014: Conversion of the two arm study design into a single arm trial (control arm only). This measure was necessary as the production of catumaxomab was discontinued.

Amendment 1 was implemented in protocol version 1.4. The amendments 2-4 had no impact on the content of the protocol. Other documents, such as the patient information and the protocol annex, were affected by these amendments. The amended documents as well as explanations concerning the changes were sent to the study centers by mail.

Protocol Version 1.2 from 08.12.2010 (protocol version at request for approval of the study by the federal authority and the ethics committee)

Protocol Version 1.3 from 24.03.2011 (protocol version after approval of the study and implementation of the changes required by the federal authority and the ethics committee)

Protocol Version 1.4 from 26.11.2012 (protocol version with implemented changes according to amendment 1)

Investigators:

No consent to use personal data - see study centres instead.

Study centre(s):

Städtisches Klinikum Braunschweig gGmbH
Medizinische Klinik III
Celler Str. 38
38114 Braunschweig

Universität Leipzig Medizinische Fakultät
Universitäres Krebszentrum Leipzig (UCCL)
Liebigstrasse 20
04103 Leipzig

Krankenhaus Nordwest GmbH

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Klinik f. Onkologie und Hämatologie
Institut für Klinische Forschung
Steinbacher Hohl 2-26
60488 Frankfurt

Charité Universitätsmedizin Berlin
Interdisziplinäres Darmzentrum der Charité
Medizinische Klinik I (Gastroenterologie, Rheumatologie, Infektiologie)
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Campus Benjamin Franklin
12200 Berlin

Klinikum der Universität zu Köln
Klinik I für Innere Medizin
Kerpener Str. 62
50937 Köln

Kliniken Nordoberpfalz AG
Klinikum Weiden, Medizinische Klinik I
Söllnerstr. 16
92637 Weiden

Universitätsklinikum Würzburg
Medizinische Klinik und Poliklinik II
Oberdürrbacher Str. 6
97080 Würzburg

Universitätsklinikum des Saarlandes
Klinik für Innere Medizin II
Kirrberger Straße, Gebäude 41
66421 Homburg/Saar

Klinikum Mutterhaus der Borromäerinnen
Akademisches Lehrkrankenhaus der Johannes Gutenberg-Universität Mainz, Innere Medizin I
Feldstraße 16
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DIAKO Ev.Diakonie-Krankenhaus gGmbH, Medizinische Klinik
Abteilung Hämatologie und Onkologie
Gröpelinger Heerstr. 406-408
28239 Bremen

Krankenhaus Barmherzige Brüder
Klinik für Internistische Onkologie und Hämatologie
Prüfeningerstr. 86
93049 Regensburg

Kliniken Essen-Mitte, Evang. Huyssens-Stiftung/Knappschaft GmbH
Akademisches Lehrkrankenhaus der Universität Duisburg-Essen, Klinik für Innere Medizin IV
Henricistraße 92
45136 Essen

Klinikum der Johann Wolfgang Goethe-Universität, Zentr. der Inneren Medizin, Medizinische Klinik I

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60590 Frankfurt am Main

Augusta-Kranken-Anstalt
Klinik für Hämatologie, Onkologie und Palliativmedizin,
Bergstraße 26
44791 Bochum

Klinikum Aschaffenburg, Medizinische Klinik II
Am Hasenkopf
63739 Aschaffenburg

Medizinische Hochschule Hannover
Kinik für Gastroenterologie, Hepatologie und Endokrinologie
Carl-Neuberg-Str. 1
30623 Hannover

Isar Medizin Zentrum, Allgemein-, Viszeral- und Tumorchirurgie
Sonnenstrasse 24-26
80331 München

Publication (reference):

NA (in prep.)

Studied period (years):	Phase of development:
20.10.2011 (date of first enrolment) 25.08.2016 (date of last completed) No formal temporary halts occurred during the course of the trial.	Phase II

Objectives:

Primary objective

The main objective of this trial was to investigate the efficacy of catumaxomab by determination of the rate of macroscopic complete remissions of peritoneal carcinomatosis after treatment with one cycle (four doses) of catumaxomab followed by six cycles of FLOT chemotherapy. The primary endpoint was the rate of macroscopic complete remissions of peritoneal carcinomatosis at the second diagnostic laparoscopy or laparotomy.

Secondary objectives

Secondary endpoints to be analyzed in both study arms, (including exploratory comparisons) were:

- Surgical resection rate (R0, R1, R2)
- Overall survival (OS)
- Disease-free survival (DFS)
- Progression-free survival (PFS)
- Immunoreaction against tumor in tissue samples
- Detection of disseminated tumor cells via PCR

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- Frequency, relationship, and severity/seriousness of AEs

Methodology:

Explorative randomized phase II study (Multicenter randomized, open-label phase II study)

Number of patients (planned and analysed):

About 42 patients (21 in the experimental and 21 in the reference arm) from about 15 German centers were initially planned.

As in June 2014 catumaxomab was no longer available, the study protocol was amended accordingly. As a result, there was a lack of recruitment and therefore the study was terminated prematurely after the recruitment of 35 patients. Data analysis was performed based on the data achieved from these 35 patients.

Diagnosis and main criteria for inclusion:

Diagnosis:
Histologically confirmed diagnosis of gastric adenocarcinoma
Macroscopic peritoneal carcinomatosis (stage P1-4 according to Gilly et al.)
Patients eligible for gastrectomy after primary systemic (and intraperitoneal) treatment

Inclusion criteria:

- Histologically confirmed diagnosis of resectable gastric adenocarcinoma or adenocarcinoma of the esophagogastric junction (type II and type III according to Siewert's classification)
- Macroscopic peritoneal carcinomatosis (stage P1-4 according to Gilly et al)
- Patients potentially eligible for gastrectomy after primary systemic (and intraperitoneal) treatment
- Signed and dated informed consent before the start of specific protocol procedures.
- Age > 18 years
- ECOG Performance Status of 0 or 1
- Body mass index (BMI) > 17
- Life expectancy of at least 12 weeks
- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening:
  - Hemoglobin > 10.0 g/dl
  - Leukocyte count >4.000/µl; absolute neutrophil count (ANC) >2.000/µl
  - Platelet count ≥ 100.000/µl
  - Total bilirubin < 1,5 times the upper limit of normal
  - ALT and AST < 3 x upper limit of normal
  - Alkaline phosphatase < 5 x ULN
  - Serum creatinine < 1.5 x upper limit of normal and creatinine clearance >60 ml/min.
- The patient is willing and able to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations.

Exclusion criteria:

- Distant metastasis other than peritoneal seedings
- Prior diagnosis of any malignancy not cured by surgery alone less than 5 years before study entry
- Clinically significant cardiovascular disease (incl. myocardial infarction, unstable angina,

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symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 1 year before enrolment

- History of HIV infection or chronic hepatitis B or C
- Active, clinically serious infections (> grade 2 NCI-CTC version 3.0)
- Pre-existing neuropathy > grade 1 (NCI CTCAE), except for loss of tendon reflex
- Quick < 70%; INR > 1.5 x upper normal limit; administration of drugs inhibiting platelet aggregation within 7 days before start of study therapy; ongoing oral anti-coagulative therapy such as Marcumar
- Patients with seizure disorder requiring medication (such as steroids or anti-epileptics)
- History of organ allograft
- Patients undergoing renal dialysis
- Known hypersensitivity to any of the drugs given in the study; knows hypersensitivity to murine (rat and/or mouse) proteins
- Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study
- Excluded therapies and medications, previous and concomitant:
  - Prior anti-cancer chemotherapy or immunotherapy
  - Investigational drug therapy outside of this trial during or within 4 weeks of strdy entry
  - Major surgery within 4 weeks of starting the study, and patients must have recovered from effects of major surgery
- Pregnant or breast-feeding patients, or planning to become pregnant within 6 month after the end of treatment. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Women enrolled in this trial must use adequate barrier birth control measures during the course of the trial and for 6 months after the end of treatment
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's understanding of the informed consent procedure, participation in the study or evaluation of the study results
- Inability of the patient to give informed consent, i.e. not fulfilling the criteria defined in the German "Arzneimittelgesetz" (§ 40 Abs. 1 Satz 3 Nr. 3 Buchstabe a)

Test product, dose and mode of administration, batch number:

Distribution and accountability:
Catumaxomab (Removab®) was delivered free of charge by Fresenius Biotech GmbH, and neovvii Biotech GmbH, respectively. In order to be able to account for the distribution and application of the drug, a detailed record had to be kept by the investigator.

Packaging and formulation:
Each prefilled syringe of catumaxomab contained 0.1 or 0.5 mL of a sterile, clear and colourless protein solution containing 10 µg or 50 µg of catumaxomab, respectively.

Labelling and storage:
Each vial of catumaxomab was labelled in accordance with current ICH GCP and specific national requirements. Catumaxomab has a shelf time of 24 months.

Dose:
Catumaxomab was administered in arm A only at doses of 10 µg, 20 µg, 50 µg, and 150 µg on days 0, 3, 7, and 10. The patients in arm A had to be hospitalized during the catumaxomab therapy period. The catumaxomab therapy was followed by 6 cycles of FLOT (cf. Reference therapy).

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Administration: intraperitoneal infusion (i.p.)

Batch numbers:
1L03-0/1, 1L03-0/2, 1M02-0/1, 1M02-0/2, 1P02-0/1, 1P02-0/2

Duration of treatment:

If feasible, the chemotherapy/antibody combination was administered until intercurrent diagnosis of disease progression (according to RECIST criteria). If not prevented by fulminating early progression or severe toxicity, a minimum of two cycles should have been applied.

Reference therapy, dose and mode of administration, batch number:

In the reference arm without prior administration of catumaxomab, patients received the same background medication as in the experimental arm, consisting of 6 cycles of FLOT therapy as follows:

Oxaliplatin: 85 mg/m², d 1
Leucovorin: 200 mg/m², d 1
5-FU: 2600 mg/m² as 24 h infusion, d 1
Docetaxel: 50 mg/m², d 1

6 cycles q 2wk

Criteria for evaluation:

Efficacy

Patients not fulfilling the selection criteria of the trial ("non-eligible") were excluded from the statistical analysis. Only case descriptions were provided for this group. The number of recruited patients was adjusted, respectively. All other patients were primarily evaluated in an intent-to-treat analysis (ITT). Sensitivity analyses of efficacy endpoints was performed on the per protocol analysis set defined as the subset of the ITT analysis set who had received the full cycle of catumaxomab therapy during the protocol treatment period, at least one chemotherapy cycle, had a second laparoscopy and who had no major protocol deviations thought to impact on the efficacy conclusions of the trial.

Safety

Evaluation of safety criteria is covered by documentation and reporting of adverse events and serious adverse events. The safety analysis comprises all patients having received at least one application of study therapy.

Statistical methods:

All parameters were evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. If any p values were calculated (e.g. in subgroup comparisons), they were considered to be descriptive and were presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing was performed. Thus the p values reflect the comparison-wise error and not the experiment-wise error. All p values are two-sided if not stated otherwise. The statistical methods described in this section are suited for the data and distributions usually expected in this type of trials. The suitability was checked

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after data entry.

Macroscopic complete remission rate of peritoneal carcinoma (primary endpoint), toxicity, response and other event rates at pre-specified time points were calculated, providing confidence intervals. In case of comparison between patient groups, these rates were analyzed by Fisher´s exact test.

Event related data like progression-free, disease-free or overall survival were estimated by the product limit method and eventually compared using the logrank test. If the Peto logrank test was not appropriate because of violation of the proportional hazard assumption, Gehan's generalization of the Wilcoxon rank sum test for censored data (GEHAN 1965) was applied, preferably in its modification by PETO (1972) and PRENTICE (1978). If appropriate, prognostic strata were taken into account.

Summary - Conclusions:

In the trial presented a total of 35 patients were recruited from October 2011 to December 2014. 31 patients were evaluable according to the ITT collective. These 31 patients were recruited by 11 of the 16 participating trial-sites. The following table shows in detail the distribution of these patients on the trial-sites:

Trial-site	**Arm A**	**Arm B**	**Total**
n	15	16	31
Würzburg	5 (33%)	3 (19%)	8 (26%)
Frankfurt Uni	3 (18%)	2 (12%)	5 (16%)
Berlin	2 (13%)	2 (12%)	4 (13%)
Regensburg	3 (20%)	1 (6%)	4 (13%)
Weiden	-	3 (19%)	3 (10%)
Braunschweig	-	2 (11%)	2 (6%)
Bochum	-	1 (6%)	1 (3%)
Essen	-	1 (6%)	1 (3%)
Frankfurt NW	1 (7%)	-	1 (3%)
Köln	1 (7%)	-	1 (3%)
Leipzig	-	1 (6%)	1 (3%)

Baseline characteristics

Just over half of the entire study population was male, but gender distribution on both therapy arms was not balanced: in the arm B, more than 60% of the patients were male, whereas approximately the same proportion of men and women were randomized into arm A.

The randomization was stratified according to the classification of the peritoneal carcinosis by Gilly stage. Approximately 60% of the total population was assigned to the stages P2 and P3. The distribution of the strata on the two therapy arms is balanced, due to the stratified randomization. Most patients suffered from a tumor of the stomach. In only a small subgroup of the study population (6 patients, 19%) the tumor was located at the gastroesophageal junction. Almost all patients of this subgroup were randomized in the comparator arm (5 patients, 31% of the patients in arm B).
At baseline the peritoneal cancer index was slightly higher in patients of the comparator arm (mean 13.1, median: 12) compared to the experimental arm (mean: 12.1, median: 8).

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Efficacy Results

The comparison of the peritoneal cancer indexes (PCI) before and after the neoadjuvant treatment showed a reduction after therapy for both trial arms. The median of the PCI after neoadjuvant therapy has decreased by half in the experimental arm (median of 8 before to 4 after therapy). In the comparator arm, the difference is markedly less pronounced (median of 12 to 10).

With regard to the primary objective "rate of macroscopic complete remissions (mCR) of the peritoneal carcinosis", the statistically promising value of > 20% was achieved in the experimental arm (27%). However, in the comparator arm this value was also almost reached (19%). The slight trend observed in favor of the experimental arm was not statistically significant. Nevertheless, the value of a mCR rate of only 5% (futility limit), derived from the pCR rate of published gastric cancer studies, was exceeded in both study arms. In summary, the overall concept of a neoadjuvant therapy of gastric carcinoma with peritoneal carcinosis can be rated as successful with regard to the achievable mCR rate.

Concerning the assessment of the total response of gastric tumor and peritoneal carcinosis, no patient achieved a complete remission. In both treatment arms, an equal PR rate of 46% was reached.

According to protocol, secondary endpoints were examined (see section "Objectives"). There were no statistically significant differences between the trial arms concerning progression free survival (arm A: 6.74 month vs. arm B: 5.39 month, p = 0.84, logrank test) and overall survival (~ 13 month in both trial arms, p = 0.82, logrank test).
With regard to the surgical resection rate, the proportion of patients with an operable tumor after the neoadjuvant treatment is higher in the experimental arm than in the comparator arm (53% vs. 31%). Nevertheless the rates of R0 resections are about equal in both therapy arms (Arm A: 33% vs. Arm B: 31%).

Safety Results

Hematologic toxicity during catumaxomab therapy:
Patients treated with catumaxomab had mild hematologic toxicities. Anemia was the only hematologic toxicity that occurred with the highest NCI grade 2 in 50% of the patients.

Non-hematologic toxicity during catumaxomab therapy:
The most common toxicities with severity 3/4 were infections, pain, as well as an increase in levels of bilirubin and GGT. In four patients (29%), toxicities observed under the catumaxomab treatment fulfilled the criteria to be rated as SAE.

Hematologic toxicity during FLOT therapy:
Anemia, leucopenia, neutropenia, and thrombopenia were recorded for both therapy arms. Severe toxicities of grade 3 anemia and leucopenia occurred only in a low number of patients of the experimental and the comparator arm. In arm A grade 3 neutropenia was more frequent compared to arm B (23% vs. 7%), whereas grade 4 neutropenia occurred in 15% of the patients of arm A and in 20% of the patients of arm B. Severe cases of thrombopenia were not reported for either of the two study arms.

Non-hematologic toxicity during FLOT therapy:
Only one grade 4 toxicity occurred (see below); a comparison of the severe toxicities of grade 3

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between the therapy arms shows somewhat more frequently chills/muscle stiffness in the experimental arm. In general, however, toxicities of grade 3 are more common in the comparator arm, especially nausea, vomiting and diarrhea, but also pruritus, febrile neutropenia, mucositis/stomatitis, and pain. As further serious side effects, iron deficiency syndrome of grade 3 occurred in arm A. In the comparator arm, one patient suffered from peritonitis with a small intestinal perforation (grade 4). The latter event fulfilled the criteria for an SAE. In therapy arm A, FLOT therapy did not result in any life-threatening, non-hematologic toxicity of NCI grade 4. A total of eight patients had SAEs under FLOT therapy. In the comparator arm SAEs were more frequent than in the experimental arm (31% vs. 21%).

Conclusion

The primary endpoint of this study was not met (complete macroscopic remissions of peritoneal carcinomatosis). A trend towards superiority of the experimental arm did not reach statistical significance (27% in arm A vs. 19% in arm B). Nonetheless, i.p. treatment with catumaxomab in this disease setting, showed an acceptable safety profile and addition of catumaxomab to 6 cycles of FLOT chemotherapy did not produce any unexpected adverse events: the toxicity profile observed in this study was roughly the same as in previous reports. There was only a trend towards more adverse events observed during FLOT chemotherapy following catumaxomab (arm A) compared with chemotherapy alone (arm B), without preventing the feasibility of systemic chemotherapy.

We have to conclude that we did not observe a major difference in survival outcomes (progression free survival in arm A: 6.74 month vs. 5.39 month in arm B and overall survival ~ 13 month in both trial arms) between the two arms, which was a secondary endpoint of this study. Of note, both the efficacy and safety assessment as well as survival analyses are limited by small patient numbers. However, the survival outcomes are within the expected range for a palliative treatment approach in patients with metastatic gastric adenocarcinoma.

In summary, the addition of catumaxomab seems feasible and tolerable in patients with advanced gastric cancer. Efficacy assessment was limited by small patient numbers. Although the primary endpoint was not met, the results are promising for future investigations integrating intraperitoneal therapy into a multimodal treatment.

Date of report:

01.06.2017