2. SYNOPSIS

Name of Sponsor/Company: AIO-Studien-gGmbH **Names of Finished Products:** Vectibix® **Names of Active Ingredients:** Panitumumab	

STUDY TITLE:
An Open Label Randomized Controlled Phase lI Trial of Panitumumab in Combination with Epirubicin, Cisplatin and Capecitabine (ECX) versus ECX Chemotherapy alone in Subjects with Locally Advanced Gastric Cancer or Cancer of the Gastroesophageal Junction

STUDY CENTRE(S):
22 study sites (hospitals and practices) in Germany were enrolling patients.

PUBLICATION(S):
In preparation

STUDY PERIOD:	**PHASE OF DEVELOPMENT:**
First patient enrolled: November 2010 End of study: March 2016	Phase II

OBJECTIVES:

Primary:
To compare the prevalence of pT3/pT4 categories between subjects receiving panitumumab plus epirubicin, cisplatin and capecitabine (ECX) versus subjects treated with ECX chemotherapy alone.

Secondary:
To compare the prevalence of pN2/N3 categories between subjects receiving panitumumab plus epirubicin, cisplatin and capecitabine (ECX) versus subjects treated with ECX chemotherapy alone. To assess if the addition of panitumumab to ECX chemotherapy increases histological complete and subtotal response rate (< 10% residual tumor), the R0 resection rate, progression-free survival time, time to relapse following surgery, time to treatment failure and overall survival in subjects with locally advanced gastric cancer or cancer of the gastroesophageal junction. To assess the overall safety and efficacy of ECX with or without panitumumab in this study population.

Exploratory:
Exploratory objectives might include investigation into potential correlations with respect to EGFR expression, detection of the functional genetic polymorphisms of the EGFR gene, EGFR gene amplification (FISH), EGFR activation detection, KRAS mutations, EGFR downstream protein and gene expression parameters, proteomics and epigenetics.

METHODOLOGY:
This was a phase II, open-label, randomized, controlled, parallel-arm, multi-centre study. Eligible subjects were enrolled and treated with neoadjuvant ECX chemotherapy ± panitumumab, surgery and adjuvant ECX chemotherapy ± panitumumab. Panitumumab was the investigational medicinal product, ECX chemotherapy was considered as background medication. Panitumumab was administered by intravenous (IV) infusion at a dose of 9 mg/kg IV once Q3W for 3 cycles (9 weeks) in the neoadjuvant and adjuvant setting in the experimental arm. Upon completion of the neoadjuvant treatment regimen, subjects were assessed by the Medical Oncologist and Onco-Surgeon. Subjects deemed ineligible for surgery discontinued the treatment phase, and returned for the short term safety follow up visit 56 ± 3 days later. All subjects were followed up until disease relapse. If subjects were deemed eligible for surgery, they proceeded to gastric or gastroesophageal resection 3-4 weeks after the last drug administration of the last chemotherapy cycle of the neoadjuvant regimen with a maximum delay of a further 2 weeks. Surgery was performed as soon as the patient was medically fit. Following surgery, subjects with R0 resection commenced with the adjuvant treatment regimen of ECX chemotherapy ± panitumumab within a maximum period of 60 days following surgical resection as soon as feasible, but depending on their individual physical and medical conditions. Subjects were treated in the adjuvant setting with 3 cycles (9 weeks) of ECX± panitumumab chemotherapy until completion of the adjuvant regimen, or until disease progression, withdrawal of consent or unacceptable toxicities. Subjects with R1, R2 resections or without any resection were treated on an individual basis as recommended by the treating physician. All subjects were to have a short term safety follow-up visit 56 ± 3 days following the end of the treatment period and a long term follow up for disease progression or relapse for at least 24 months.

NUMBER OF PATIENTS:

Planned Sample Size*:*

Approximately 170 evaluable subjects were required for the analysis according to sample size calculation.

Actual Sample Size:

A total of 171 patients were enrolled between November 2010 and July 2013.

DIAGNOSIS AND MAIN INCLUSION CRITERIA:

Male and female subjects suffering from locally advanced gastric cancer or cancer of the gastroesophageal junction were eligible to participate in the study if they met all selection criteria listed below.

Inclusion Criteria

Ethical

- Competent to comprehend, sign, and date an IEC-approved informed consent form, written informed consent.

Demographic

- Of either gender and aged 18 years or more.

Disease-related

- Diagnosed with histologically confirmed adenocarcinoma of the stomach or the gastroesophageal junction of Type I/II/III according to the classification of Siewert *et al*, 1996 (see Appendix 16.1.1, study protocol [appendix E]).
- Stage uT/3 or 4 N0/+ and M0 (see study protocol appendix F) disease evaluated by endoscopic ultrasound, spiral computed tomography of the chest, abdomen and pelvis, and by laparoscopy.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see study protocol appendix D).

Laboratory

- Haematologic function, as follows (within 7 days of randomisation):
  - o Leucocyte count > 4,000/mm³
  - o Platelet count ≥100,000/mm³
  - o Haemoglobin ≥10 g/dl
- Renal function, as follows (within seven days of randomisation):
  - o Serum creatinine ≤ 1.5x of upper limit of normal (ULN)
  - o Creatinine clearance > 60 ml/kg/min measured either by 24-h urine sampling or calculated by using the Cockgroft-Gault formula .
- Hepatic function, as follows (within seven days of randomisation):
  - o Aspartate aminotransferase (AST) ≤3 x ULN
  - o Alanine aminotransferase (ALT) ≤3 x ULN
  - o Bilirubin ≤ 1.5 x ULN
- Metabolic function, as follows (within 7 days of randomisation):
  - o Magnesium ≥ lower limit of normal.
  - o Calcium ≥ lower limit of normal.

General

- Subject was deemed a good candidate for surgery.

Exclusion Criteria

Disease Related

- Any metastatic disease.
- Other malignant tumors less than five years old. Exceptions include basocellular carcinoma, *in situ* cancer of the cervix of the uterus, or any curatively-treated other malignancies without evidence of disease for more than five years.
- Malignant ascites or pleural effusion.

Therapies

- Prior anti-EGFR antibody therapy (e.g. cetuximab) or treatment with small molecule EGFR tyrosine kinase inhibitors (e.g. erlotinib).
- Prior chemotherapy, previous surgical resection of gastric cancer, radiotherapy or antibody therapy for gastric cancer or cancer of the gastro-oesophageal junction.
- Concomitant therapy with sorivudine or analogue compounds.
- Known previous or ongoing abuse of narcotic drug, other medication or alcohol.

General

- Significant cardiovascular disease including New York Heart Association (NYHA) grade II or greater congestive heart failure, peripheral arterial occlusive disease stage II or greater, symptomatic coronary heart disease, insufficiently treated arterial hypertension, unstable angina or myocardial infarction within 12 months before initiating study treatment or a history of ventricular arrhythmia.

- History or evidence upon physical examination of CNS disease unless adequately treated, seizure not controlled with standard medical therapy, or history of stroke.
- History of interstitial pneumonitis or pulmonary fibrosis or evidence of interstitial pneumonitis or pulmonary fibrosis on baseline chest CT scan.
- Pre-existing polyneuropathy grade >1 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), except for loss of tendon reflex as the only symptom.
- Treatment for systemic infection within 14 days before initiating study treatment.
- Active inflammatory bowel disease, serious gastric ulceration or other bowel disease causing chronic diarrhoea (defined as > 4 loose stools per day).
- Suspected or known dihydropyrimidine dehydrogenase deficiency (DPD).
- Thrombosis or severe bleeding within six months prior to entry into the study (except for bleeding of the tumor before its surgical resection), evidence of bleeding diathesis or coagulopathy, or current or recent (within 10 days prior to initiation of study treatment) use of full-dose oral or parenteral anticoagulants for therapeutic purposes.
- History of any medical condition that might increase the risks associated with study participation or might interfere with the interpretation of the study results.
- Known positive test for human immunodeficiency virus infection, hepatitis C virus or chronic active hepatitis B infection.
- Known allergy to the investigational product, to any of its excipients, to monoclonal antibodies, or to any of the components of the chemotherapy regimen.
- Any co-morbid disease that would increase risk of toxicity.
- Any kind of disorder that compromised the ability of the subject to give written informed consent and/or comply with the study procedures.
- Any investigational agent or participation in another clinical trial within 30 days prior to randomisation.
- Must not have had a major surgical procedure within 28 days of randomisation.
- Subject who was pregnant or breast feeding.
- Woman or man of childbearing potential not consenting to use adequate contraceptive precautions (intrauterine contraceptive device, contraceptive implants, injectables (hormonal depot), transdermal hormonal contraception (contraceptive patch), sexual abstinence or vasectomised partner) during the course of the study and for six months after the last study drug administration for women and men. Post-menopausal women had to be amenorrheic for at least 12 months to be considered of non-child-bearing potential.
- Subject unwilling or unable to comply with study requirements.
- Hearing impairment

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION :

Panitumumab (Vectibix®), 9mg/KG bodyweight, intravenous, every three weeks

REFERENCE PRODUCT, DOSE AND MODE OF ADMINISTRATION :

No reference product used

Backbone standard chemotherapy (both arms):

Epirubicin, 50 mg/m² BSA, intravenous, every three weeks

Cisplatin, 60 mg/m² BSA, intravenous, every three weeks

Capecitabine 625 mg/m² BSA, per os, twice daily

DURATION OF TREATMENT:

Protocol treatment lasted up to approximately 7 months

CRITERIA FOR EVALUATION:

Primary Efficacy Endpoints:

- Proportion of patients with pT3/T4 categories after surgery. Subjects prematurely discontinuing without a post-surgical tumor response assessment were to be considered as non-responders.

Secondary Efficacy Endpoints:

- See above under "objectives"

STATISTICAL METHODS:

The primary endpoint, difference in frequencies of pT3/T4 categories between the two treatment arms was analysed using a one-sided contingency table test. A total sample size of 140 subjects provided approximately 80% power to detect a 20 percentage points difference in pT3/T4 categories at a 5% one-sided significance level, based on a chi-square test. A pT3/T4 prevalence of 75% was thought to be achievable in the ECX alone treatment arm of the study. Patients not fulfilling the selection criteria of the trial ("non-eligible") were to be excluded from the statistical analysis. Only case histories were provided for this group.

The primary analysis of efficacy endpoints were performed on the **intention-to-treat (ITT) Analysis Set** defined as all subjects who provided informed consent and were randomised to receive either

ECX+panitumumab or ECX alone, regardless of whether or not they actually received any doses of study treatment or chemotherapy, and who experienced no critical protocol violation thought to severely impact on the efficacy conclusions of the trial.. Individual subjects with missing evaluation of the pT category (due to drop out) were set as pT3/T4 and therefore conservatively treated as non-responders. Sensitivity analyses of efficacy endpoints were performed on the **Per Protocol Analysis Set** defined as the subset of the ITT analysis set who received at least one dose of drug during the study, had at least one evaluable tumor assessment and who had no major protocol deviations thought to impact on the efficacy conclusions of the trial. The **Resection Analysis Set** was defined as the subgroup of subjects in the ITT analysis set who underwent a R0 resection during the study. The latter was the primary analysis set for the time from surgery to disease relapse endpoint. Safety analyses were performed using the **All Treated** analysis set, defined as subjects in the ITT analysis set who had received at least one dose of any constituent of ECX or panitumumab.

All efficacy endpoints were reported for subjects using descriptive statistics including point estimates with 95% confidence intervals. The Kaplan-Meier method was applied to analyse event-related data from longterm follow-up.

All parameters were evaluated in an explorative or descriptive manner, in case of continuous type providing means, medians, ranges, standard deviations and/or confidence intervals, as appropriate. Response or staging rates (including the primary endpoint), toxicity, and event rates at pre-specified time points were calculated as proportions, providing confidence intervals, as appropriate. In case of comparisons between patient groups, these rates were analysed by Fisher´s exact test, χ^2 test or Mantel-Haenszel test (or trend test according to Cochran/Armitage), respectively. Event related data like relapse-free or overall survival were estimated by the product limit method and eventually compared by the logrank test.

If any p values were calculated (e.g. in subgroup/prognostic comparisons), in addition to the primary hypothesis test, 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 were two-sided if not stated otherwise.

SUMMARY – CONCLUSIONS

Patients

Between November 2010 and July 2013, 171 patients from 22 German centres were randomly assigned to receive either ECX with (N=84) or without panitumumab (N=87). Out of these, 160 patients were defined eligible for the study; 80 in ECX+P and 80 in ECX. Known prognostic factors were generally well balanced between arms.

Preoperative treatment and its safety

Of the 80 eligible patients allocated to ECX+P, 66 (82%) received all three planned cycles of chemotherapy prior to surgery as did 67/80 patients (84%) to ECX arm. As anticipated, toxicity was somewhat higher in the ECX+P arm. One patient in the chemotherapy-alone arm died from cardiac arrest during preoperative chemotherapy

Results at surgery, incl. the primary endpoint

Seventy-five and 74 patients, respectively underwent surgery in the ECX+P and ECX arms after a median time of 91 days (87 vs. 93 days) from the start of preoperative treatment. More than 90% of the patients received extended (D2) lymphadenectomy. The number of patients with distinctive lymph node involvement (more than 20% of removed lymph nodes) was higher in the experimental arm (32% vs. 21%).

The primary endpoint of the trial was not met. Adding panitumumab to ECX did not decrease the rate of failure of preoperative therapy (75% vs. 70%, p=0.28). The number of pathohistological non-responders in patients with tumor resection was not reduced (ypT3-4: 73% vs. 68%, p=0.28). Neither the rate of major histological response (grade 1a+1b: 22% vs. 16%), nor the rate of tumor free lymph nodes (37% vs. 42%) was significantly increased.

Postoperative course

Forty out of 80 eligible patients started postoperative chemotherapy in both arms at a median of 48 days (46 vs. 52 days) after surgery and 26 (65%) vs. 32 (80%) patients were able to undergo all planned cycles.

Survival outcomes

There was no significant difference in progression-free survival (PFS) between the arms with and without panitumumab, with a median PFS of 27.7 vs. 33.5 months, respectively (HR 1.19, 95% confidence interval

[CI] 0.76–1.88, p=0.45). Overall survival (OS) was also not significantly different between treatment arms. A median survival time of 35.7 months was calculated in ECX+P and was not reached in ECX. The OS at 3 years was 49% and 62% in ECX+P and ECX, respectively (HR 1.37, 95% CI 0.84–2.25, p=0.20).

Conclusion:
The results of this study suggest that adding panitumumab to the standard chemotherapy of ECX does not improve efficacy in the (neo)adjuvant treatment of patients with locally advanced gastric cancer or cancer of the gastroesophageal junction .