Stadium II/III Adenokarzinom des Magens oder gastroösophagealen Übergangs – neoadjuvante/perioperative Therapie

AIO-STO-0310 Multicenter, explorative phase II study of perioperative 5-FU, leucovorin, docetaxel, and oxaliplatin (FLOT) in combination with trastuzumab in patients with HER2 positive, locally advanced, resectable adenocarcinoma of the gastroesophageal junction or stomach (HerFLOT)

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Indication Locally advanced, resectable adenocarcinoma of the gastroesophageal junction or the stomach

Type to study Explorative, multicenter phase II study on (neo)-adjuvant therapy

Primary endpoint To determine the rate of complete pathological responses (percentage of patients with pCR referring to the total number of enrolled and eligible patients), as evaluated centrally by a reference pathologist

Secondary endpoints • R0 resection rate • Relapse-free survival • Overall survival, including survival rates after 1, 2 and 3 years • Evaluation of pCR as a surrogate endpoint

Secondary objectives • Evaluation of prognostic and predictive markers • To describe perioperative morbidity and mortality • To describe safety and tolerability of the trastuzumab/FLOT regimen

Study design Patients with HER2 neu positive locally advanced, resectable (T2-4 and/or N+, M0) adenocarcinoma of the stomach or gastroesophageal junction without pre-treatment are eligible for the study. An initial staging in order to exclude distant metastases is performed, including a CT of thorax and abdomen. The locoregional tumor spread is determined according to recommendations of the S3 guideline using EUS. Moreover, the exclusion of peritoneal carcinomatosis by laparoscopy is recommended. Subsequently, the patients receive four pre-operative cycles of FLOT in combination with trastuzumab. Thereafter, another clinical tumor staging by CT is performed before surgery. Within 6 to 8 weeks after the resection, the administration of four additional cycles of FLOT/trastuzumab is started followed by 9 cycles of trastuzumab monotherapy. In case of new evidence (i.e. studies in early breast cancer indicating that 6 months of trastuzumab may replace the 12-months treatment) it will be considered for the Her-FLOT study to reduce the treatment duration for trastuzumab by a protocol amendment. The complete pathological remission rate is determined by central review (primary endpoint).

The objective of this explorative phase II study is to improve the rate of complete pathological remissions (pCR) by 100% compared to a patient population which was treated with FLOT alone in a parallel study (FLOT-4). Both study populations are examined in a standardized way by a reference pathologist.
Secondary endpoints include the assessment of relapse-free and overall survival. Radiological slice tomography (CT or MRT of thorax and abdomen) are performed for staging at baseline and every 3 months after surgery until relapse of disease or death of the patient. The follow up duration with respect to relapse-free survival and for overall survival is 2 years after end of treatment. During chemotherapy, clinical visits (blood cell counts, detection of toxicity, patient interview) occur every two weeks.

Rationale

The addition of trastuzumab to a standard chemotherapy consisting of cisplatin and 5-FU/capecitabine resulted in a significant increase in overall survival and response rate in patients with advanced HER2 neu positive gastric cancer. FLOT is established as a highly active and well tolerable regimen in the treatment of advanced cancer of the gastroesophageal junction or the stomach. Its tolerability and efficacy has likewise been shown in the neoadjuvant setting (data on file). Within the framework of the AIO FLOT 4 study, the FLOT regimen is currently compared against another present standard for perioperative treatment, ECF. In this trial the HER2 status is not a selection criterion for patient inclusion. The primary objective of AIO FLOT 4 is the rate of complete pathological responses (pCR); secondary criteria include overall survival and progression-free survival. The correlation between pCR after neoadjuvant treatment and increased overall survival has been shown in other malignancies, e.g. breast cancer, but not yet in gastric cancer. Thus, in addition to the comparison of the chemotherapy regimens, the assessment of an influence of achieving a pCR on the long term outcome is a major objective of AIO FLOT 4. In this trastuzumab/FLOT study, the HER2-targeted monoclonal antibody will be added to the FLOT chemotherapy backbone. As a sufficiently large study population with positive HER2 status and a neoadjuvant treatment situation, allowing to embark on a randomized phase III study (e.g. FLOT with vs. without trastuzumab) cannot be recruited within a reasonable time period, the HER2 positive subpopulation of the AIO FLOT 4 study will serve as a control group, recruited in the same collaborative group centers. At the presumed time point of initiation of the present study, the majority of the patients in AIO FLOT 4 will probably be recruited.

The FLOT regimen is chosen as chemotherapy backbone, firstly, because a combination of trastuzumab and anthracycline-containing chemotherapy (such as ECF) is not recommended due to the overlapping cardiotoxicity, and secondly, because of the availability of comparable subjects and identical standardized assessment methods in the FLOT 4 study.

To improve the prediction of the individual response to a treatment with trastuzumab prognostic and predictive markers will be analysed in the translational research programme, which is an essential part of the protocol.

Inclusion criteria

- Histologically confirmed adenocarcinoma of the gastroesophageal junction (AEG I-III) or the stomach (uT2, uT3, uT4, any N category, M0), or any T N+ M0 patient, with the following specifications:
  - Endosonography and an esophageal-gastro-duodenoscopy
  - Categorization of gastroesophageal junction tumors according to the classification by Siewert (1987, cf. appendix 2)
- Detection of an adenocarcinoma with HER2 3+ (IHC) or HER2 2+ (IHC) with amplification proven by FISH, SISH or CISH by an accredited local pathologist (for quality assurance tumor samples have to be available for a subsequent central review)
- No preceding cytotoxic or targeted therapy
- Male and female patients aged ≥ 18 years. If able to reproduce, patients must be willing to use highly effective methods of contraception during treatment and for 6 months after the end of treatment (adequate: methods fulfilling the requirements of the Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals [CPMP/ICH/286/95 mod]). Female patients with reproductive ability must have performed a negative pregnancy test within 7 days of study entry.
**Exclusion criteria**

- Known hypersensitivity against trastuzumab, murine proteins, 5-FU, leucovorin, oxaliplatin or docetaxel
- Other known contraindications against trastuzumab, 5-FU, leucovorin, oxaliplatin, or docetaxel
- Clinically significant active coronary heart disease, cardiomyopathy or congestive heart failure, NYHA III-IV
- Clinically significant valvular defect
- Past or current history of other malignancies not curatively treated and without evidence of disease for more than 5 years, except for curatively treated basal cell carcinoma of the skin and in situ carcinoma of the cervix
- Known brain metastases
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy
- Other severe internal disease or acute infection
- Peripheral polyneuropathy > NCI Grade II
- Chronic inflammatory bowel disease
- On-treatment participation in another clinical study in the period 30 days prior to inclusion and during the study
- Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment.
- Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)
- Any other concurrent antineoplastic treatment including irradiation

**Treatment scheme**

**FLOT - trastuzumab**

- Trastuzumab 4 mg/kg BW (6 mg loading dose at 1st administration), iv over 1 h, d1
- Docetaxel 50 mg/m², iv over 2 h, d1
- Oxaliplatin 85 mg/m² in 500 ml G5%, iv over 2h, d1
- Leucovorin 200 mg/m² in 250 ml NaCl 0,9%, iv over 1 h, d1
- 5-FU 2600 mg/m², iv over 24 h, d1

(= 1 cycle)

Start of next cycle on day 15

**Trastuzumab monotherapy**

- Trastuzumab 6 mg/kg BW, iv over 1 h, d1

(= 1 cycle)

Start of next cycle on day 22

**4 pre-operative cycles (8 weeks)** (surgery recommended to start 3 weeks after end of last preoperative cycle), **4 post-operative cycles (8 weeks)** (recommended to be started 6 to 8 weeks, max. 12 weeks after surgery) and **9 additional post-operative cycles of trastuzumab monotherapy (27 weeks)**.

Patients, which prove to be ineligible for post-operative chemotherapy, may switch to trastuzumab monotherapy (6 mg/kg BW) every 3 weeks (1 cycle = 21 days) instead of post-operative chemotherapy for 8 weeks (1 cycle = 14 days) before entering into the regular trastuzumab monotherapy delivered every 3 weeks.
According to the existing evidence, a complete pathological response rate of 10% is assumed to be achieved by combination chemotherapy alone.
- Consequently, the experimental therapy arm with trastuzumab would be rated as insufficiently effective if the observed pCR rate is 10% or lower, as this corresponds to the efficacy of the standard treatment.
- On the other hand, the experimental therapy would be considered to be a highly promising candidate for further development (e.g. in a randomized phase III trial), if the true pCR rate is doubled to 20% or more.
- Probability that the experimental therapy would be accepted as promising (> 20% pCR rate) with respect to efficacy, in spite of a true pCR rate of ≤ 10%: 10% (type I error)
- Probability that the experimental therapy would be rejected as not sufficiently effective (≤ 10%) although the true pCR rate is promising (> 20%): 20% (type II error, corresponding to a power of 80%)
This results in a sample size requirement of **53 evaluable patients**, based on a single-stage design for phase II studies by FLEMING (1982).
Interim assessment of feasibility is performed on a frequent schedule. A formal interim analysis is performed after a safety run in phase of the first 20 patients and reviewed by an external data and safety monitoring board (DSMB). Descriptive statistical methods are used in this study.

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| Number of centers | 30, in order to screen about 265 patients (and assuming a HER2 positivity rate of 20%).  
The study is open for participation of further centers, please contact the AIO-Studien-gGmbH. |
| Study participation |  |
| Study duration | Approx. 24 months of recruitment; 3 years of additional follow-up |