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)

- Study Protocol -

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# TABLE OF CONTENTS

**STUDY SYNOPSIS** .......................................................................................................................... 1

1 SCIENTIFIC BACKGROUND AND RATIONALE ........................................................................ 8

1.1 Gastric cancer ................................................................................................................................ 8

1.1.1 General aspects ......................................................................................................................... 8

1.1.2 Treatment of locally advanced gastric cancer ......................................................................... 8

1.1.3 Novel cytostatic agents in the treatment of advanced gastric cancer ....................................... 9

1.1.3.1 Oxaliplatin as alternative to cisplatin ...................................................................................... 9

1.1.3.2 Taxanes as a third drug ........................................................................................................... 9

1.1.3.3 The FLOT combination ......................................................................................................... 10

1.2 Trastuzumab (Herceptin®) and its HER2 target ........................................................................ 11

1.2.1 The HER2 target in oncology .................................................................................................. 11

1.2.2 HER2-targeted treatment ......................................................................................................... 11

1.2.3 HER2 and trastuzumab in gastric cancer ................................................................................... 12

1.2.4 Duration of trastuzumab treatment .......................................................................................... 13

1.3 Rationale of the study ................................................................................................................... 14

2 STUDY OBJECTIVES ..................................................................................................................... 15

2.1 Primary endpoint .......................................................................................................................... 15

2.2 Secondary objectives and endpoints .......................................................................................... 15

3 STUDY DESIGN ............................................................................................................................... 16

3.1 Type of study ............................................................................................................................... 16

3.2 Patient number ............................................................................................................................ 16

3.3 Time schedule ............................................................................................................................. 16

3.4 Number of Centers ...................................................................................................................... 16

4 PATIENT SELECTION ..................................................................................................................... 16

4.1 Inclusion criteria .......................................................................................................................... 16

4.2 Exclusion criteria ......................................................................................................................... 17

5 TREATMENT ..................................................................................................................................... 19

5.1 Overview ....................................................................................................................................... 19

5.2 Treatment scheme ....................................................................................................................... 20

5.2.1 FLOT - trastuzumab .................................................................................................................. 20

5.2.2 Trastuzumab monotherapy ..................................................................................................... 20

5.2.3 Additional trastuzumab monotherapy ....................................................................................... 20

5.3 Study medication ......................................................................................................................... 21
5.3.1 Distribution and accountability of study medication .................................................. 21
5.3.2 General information on the study medication ......................................................... 21
5.3.3 Docetaxel .................................................................................................................. 21
  5.3.3.1 Formulation ............................................................................................................ 21
  5.3.3.2 Dispensing ............................................................................................................. 21
  5.3.3.3 Handling precautions ............................................................................................ 22
  5.3.3.4 Possible adverse effects ....................................................................................... 23
5.3.4 Oxaliplatin ................................................................................................................. 23
  5.3.4.1 Formulation ............................................................................................................ 23
  5.3.4.2 Dispensing ............................................................................................................. 23
  5.3.4.3 Handling precautions ............................................................................................ 23
  5.3.4.4 Possible adverse effects ....................................................................................... 23
5.3.5 5-Fluorouracil / leucovorin ....................................................................................... 24
5.3.6 Trastuzumab .............................................................................................................. 24
  5.3.6.1 Distribution and accountability ............................................................................ 24
  5.3.6.2 Packaging and formulation .................................................................................. 24
  5.3.6.3 Labelling and storage .......................................................................................... 25
  5.3.6.4 Preparation and administration ......................................................................... 25
  5.3.6.5 Possible adverse effects ....................................................................................... 25
5.4 Modifications of therapy and dosage ........................................................................... 26
  5.4.1 General remarks ..................................................................................................... 26
  5.4.2 Modifications of chemotherapy .............................................................................. 27
    5.4.2.1 Dose adjustment/delay in case of hematotoxicity .................................................. 27
    5.4.2.2 Dose adjustment in case of diarrhea / mucositis .................................................. 27
    5.4.2.3 Dose adjustment in case of oxaliplatin neurotoxicity ............................................. 27
    5.4.2.4 Dose adjustment in case of nephrotoxicity .......................................................... 28
    5.4.2.5 Dose adjustment in case of other toxicities .......................................................... 28
  5.4.3 Modifications of trastuzumab treatment ................................................................. 28
    5.4.3.1 Interruption of trastuzumab infusion ................................................................. 28
    5.4.3.2 Trastuzumab dosage adjustments ...................................................................... 29
5.5 Precondition for start of a new treatment cycle .............................................................. 29
5.6 Compliance .................................................................................................................. 29
5.7 Concomitant and supportive treatment ........................................................................ 30
  5.7.1 General aspects ....................................................................................................... 30
  5.7.2 Pre-treatment ......................................................................................................... 30
  5.7.3 Treatment of nausea/vomiting ................................................................................ 30
  5.7.4 Treatment of diarrhea ............................................................................................ 30
  5.7.5 Prevention and treatment of neutropenia ............................................................... 32
5.8 Surgical procedures ..................................................................................................... 32
  5.8.1 General aspects ....................................................................................................... 32
  5.8.2 Technique of esophagectomy with lymph node dissection in AEG type I tumors .... 33
  5.8.3 Technique of total gastrectomy with D2-lymphadenectomy for carcinoma of the gastric corpus (middle gastric third) .................................................. 33
  5.8.4 Technique of transhiatally extended total gastrectomy with extended D2-lymphadenectomy for carcinoma of the cardia or subcardial region (oral gastric third) .............. 34
5.8.5 Technique of total gastrectomy with extended D2-lymphadenectomy for carcinoma of the gastric antrum (distal gastric third) ................................................................. 34
5.8.6 Reconstruction ........................................................................................................ 35
5.8.7 Instructions for the preparation of resected material by the pathologist .............. 35
5.9 Emergency management ........................................................................................... 36
5.10 Enrolment ................................................................................................................ 36
5.11 Premature withdrawal of an individual subject .......................................................... 37
5.12 Premature study termination by the sponsor, the coordinating investigator, the competent authority and the ethics committee ......................................................... 37

6 STUDY ASSESSMENTS AND CRITERIA OF EVALUATION ........................................ 39
6.1 Overview / schedule of study assessments ................................................................. 39
6.2 Assessments at recruitment ....................................................................................... 40
6.3 Assessments during and after study treatment .......................................................... 41
6.4 Follow-up documentation ....................................................................................... 43
6.5 Criteria for efficacy evaluation ................................................................................ 44
6.5.1 Tumor evaluations ................................................................................................. 44
6.5.2 Perioperative morbidity and mortality .................................................................... 44
6.5.3 Relapse-free survival .............................................................................................. 45
6.5.4 Overall survival ..................................................................................................... 45
6.6 Criteria for safety evaluation ................................................................................... 45
6.6.1 Toxicity / adverse events (AE) ............................................................................... 45
6.6.2 Serious adverse events (SAE) / SUSAR ................................................................. 46
6.6.3 Methods of recording and assessing adverse events .............................................. 47
6.6.4 Procedure for reporting serious adverse events .................................................... 49
6.6.5 Pregnancy Reporting ............................................................................................ 50
6.6.6 Monitoring of subjects with adverse events .......................................................... 50
6.6.7 Overdose ................................................................................................................ 51

7 DATA MANAGEMENT UND STATISTICAL ASPECTS ............................................. 51
7.1 Data management ...................................................................................................... 51
7.2 Biostatistical aspects ................................................................................................. 51
7.2.1 General design ..................................................................................................... 51
7.2.2 Sample size calculation ....................................................................................... 51
7.2.3 Evaluation categories of patients .......................................................................... 52
7.2.4 Statistical methods ............................................................................................... 53
7.2.5 Interim and final analyses ................................................................................... 53

8 STUDY DOCUMENTATION AND ARCHIVING .................................................... 54
8.1 Documentation and information flow ...................................................................... 54
8.2 Data archiving .......................................................................................................... 55

9 FINANCING ................................................................................................................... 56
10 USE OF INFORMATION AND PUBLICATION ................................................................. 56

11 ETHICAL AND LEGAL REQUIREMENTS ................................................................. 57

11.1 General requirements and agreements ............................................................... 57
11.2 Declaration of Helsinki ......................................................................................... 58
11.3 Informed consent of the patient ......................................................................... 58
11.4 Quality assurance ................................................................................................. 59
11.4.1 Standardisation ................................................................................................. 59
11.4.2 Monitoring / source data verification ............................................................... 59
11.4.3 Audits ................................................................................................................. 60
11.5 Registration and request for authorisation of the trial ........................................... 60
11.6 Ethical committee ................................................................................................. 60
11.7 Protocol amendments ......................................................................................... 61
11.8 Subject insurance ................................................................................................. 61
11.9 Information on study drugs to trial investigators .................................................. 62
11.10 Independent Data Monitoring Committee (IDMC) .............................................. 62

12 REFERENCES ........................................................................................................... 62

APPENDICES

1 RECIST Criteria V. 1.1, 2009
2 Siewert Classification of cancers of the gastroesophageal junction, 1987
3 NCI CTCAE V. 4
4 Summary of Product Characteristics (SmPC)
5 Declaration of Helsinki, 1996
6 Central pathology
7 Rüschoff SOPs
8 Translational Research

ABBREVIATIONS

AE Adverse Event
AEG Adenokarzinom des Ösophagogastralen Übergangs
AIO Arbeitsgemeinschaft Internistische Onkologie
AMG Arzneimittelgesetz
AP alkaline Phosphatase
AST/ALT Aspartate aminotransferase (=sGOT)/ Alanine Aminotransferase (=sGPT)
BW Body Weight
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CR</td>
<td>Complete Response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>CT</td>
<td>Computer Tomographie</td>
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<tr>
<td>CTC/CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
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<tr>
<td>DCF</td>
<td>Docetaxel + Cisplatin + 5- Fluorouracil</td>
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<tr>
<td>DFS</td>
<td>Disease Free Survival</td>
</tr>
<tr>
<td>DLT</td>
<td>Dose Limiting Toxicity</td>
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<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<tr>
<td>DNA</td>
<td>Desoxyribonucleinacid</td>
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<tr>
<td>EKG</td>
<td>Elektrokardiogram</td>
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<tr>
<td>ECF</td>
<td>Epirubicin, Cisplatin und 5-FU</td>
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<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>ECX</td>
<td>Epirubicin, Cisplatin and Xeloda (Capecitabin)</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for the Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal Growth Factor Receptor</td>
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<tr>
<td>5-FU</td>
<td>5-Fluorouracil</td>
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<tr>
<td>FLOT</td>
<td>5-FU, Leucovorin, Oxaliplatin and Taxotere (Docetaxel)</td>
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<tr>
<td>GC</td>
<td>Gastric Cancer</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>G-CSF</td>
<td>Granulocyte Colony-Stimulating Factor</td>
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<tr>
<td>GI</td>
<td>Gastro-Intestinal</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
</tr>
<tr>
<td>i.v.</td>
<td>intravenous</td>
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<tr>
<td>KCI</td>
<td>Kaliumchlorid</td>
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</tbody>
</table>
kg  Kilogramme

KHK  koronare Herzerkrankung

LAD  Lymphadenektomie

LKP  Leiter der klinischen Prüfung

MMP9  Matrix-Metalloproteinase 9

mRNA  messenger Ribonucleinsäure

MR  minor response

MRT  Magnet Resonanz Tomographie

mg  Milligramme

m2  Square meter

ml  Milliliter

µl  Mikroliter

NaCl  Natriumchlorid

NC  no change

NCI  National Cancer Institute

nl  Nanoliter

NYHA  New York Heart Association

OS  Overall Survival

pCR  Pathological Complete Response

PD  Progressive Disease

PFS  Progression Free Survival

p.o.  Oral administration

PR  Partial Response

RECIST  Response Evaluation Criteria in Solid Tumours

RT-PCR  reverse transcriptase polymerase chain reaction
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>RR</td>
<td>Response rate</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>s.c.</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SD</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operation Procedure</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TNM</td>
<td>Primary tumor/regional Lymph node/distant metastasis</td>
</tr>
<tr>
<td>TTP</td>
<td>Time to Tumour Progression</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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</table>
**STUDY SYNOPSIS**

<table>
<thead>
<tr>
<th><strong>Title of Study</strong></th>
<th>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)</th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Locally advanced, resectable adenocarcinoma of the gastroesophageal junction or the stomach</td>
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<tr>
<td><strong>Type to study</strong></td>
<td>Explorative, multicenter phase II study on (neo)-adjuvant therapy</td>
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<tr>
<td><strong>Primary endpoint</strong></td>
<td>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</td>
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</table>
| **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
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.
- ECOG ≤ 2
- Exclusion of distant metastasis by CT of thorax and abdomen, bone scan or MRI (if osseous lesions are suspected due to clinical signs)
- Laparoscopic exclusion of peritoneal carcinomatosis, if suspected clinically
- Adequate haematological, hepatic and renal function parameters:
  - Leukocytes ≥ 3000/mm³, platelets ≥ 100,000/mm³
  - Serum creatinine ≤ 1.5 x upper limit of normal, or
<table>
<thead>
<tr>
<th><strong>Perioperative FLOT and Trastuzumab in locally advanced, resectable gastric cancer</strong></th>
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<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>GFR &gt; 40 ml/min</td>
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<tr>
<td>Bilirubin ≤ 1.5 x upper limit of normal, AST and ALT ≤ 3.5 x upper limit of normal, alkaline phosphatase ≤ 6 x upper limit of normal</td>
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<tr>
<td>• Written patient consent form</td>
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<td>• Normal cardiac ejection fraction, as assessed by echocardiography</td>
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<tr>
<td><strong>Exclusion criteria</strong></td>
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<tr>
<td>• Known hypersensitivity against trastuzumab, murine proteins, 5-FU, leucovorin, oxaliplatin or docetaxel</td>
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<tr>
<td>• Other known contraindications against trastuzumab, 5-FU, leucovorin, oxaliplatin, or docetaxel</td>
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<td>• Clinically significant active coronary heart disease, cardiomyopathy or congestive heart failure, NYHA III-IV</td>
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<tr>
<td>• Clinically significant valvular defect</td>
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<td>• 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</td>
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<td>• Known brain metastases</td>
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<td>• Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy</td>
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<tr>
<td>• Other severe internal disease or acute infection</td>
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<tr>
<td>• Peripheral polyneuropathy &gt; NCI Grade II</td>
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<tr>
<td>• Chronic inflammatory bowel disease</td>
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<td>• On-treatment participation in another clinical study in the period 30 days prior to inclusion and during the study</td>
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<tr>
<td>• Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment.</td>
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<td>• Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)</td>
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<tr>
<td>Treatment scheme</td>
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<tr>
<td>Trastuzumab monotherapy</td>
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**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). Not administered post-op. chemotherapy cycles will be replaced by additional trastuzumab monotherapy cycles according to protocol section 5.2.3.

**Sample size justification / statistical methods**

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,

- Any other concurrent antineoplastic treatment including irradiation
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.

| Estimated number of centers | 30, in order to screen about 265 patients (and assuming a HER2 positivity rate of 20%) |
| Study duration              | Approx. 24 months of recruitment; 3 years of additional follow-up |
1 SCIENTIFIC BACKGROUND AND RATIONALE

1.1 GASTRIC CANCER

1.1.1 General aspects

Although the incidence of gastric cancer was declining in the Western developed countries throughout the 20th century, it remains the fourth most common cancer type worldwide with up to one million new cases per year, and the second leading cause for cancer mortality. In Germany, the yearly incidence amounts to about 20,000 men and women. Unfortunately, the majority of the cases are diagnosed at a stage that is not amenable to curative surgery. Overall, more than 80% die due to their cancer, half of those with initially unresectable disease, the other half relapsing, even though R0 resection is often achieved. The 5-year survival rate drops from more than 80% in stage IA to less than 10% in stage IV.

1.1.2 Treatment of locally advanced gastric cancer

Partial or total gastric resection remains the only form of curative treatment for gastric and gastroesophageal junction cancers, but is associated with a high rate of locoregional or distant recurrence. Therefore, numerous attempts have been undertaken during the last three decades to improve the treatment results by adding adjuvant or neoadjuvant systemic therapy, or both.

While almost all of the individual studies on adjuvant treatment could not show a significant chemotherapy effect, there was a positive trend in most of the trials. Two subsequently performed meta-analyses revealed a moderate, though significant overall survival improvement in the pooled estimates. Recently, a Japanese phase III study on the oral fluoropyrimidine S-1 showed a significant survival benefit, but this is probably not to be generalized to non-Asian populations.

Pre-operative (neoadjuvant) chemotherapy has been used for several years as a means down-staging gastric and gastroesophageal cancers prior to resection and to eliminate micrometastases. A major breakthrough was achieved by the MAGIC trial, exploring perioperative (i.e. neoadjuvant plus adjuvant) chemotherapy with infused epirubicin, cisplatin, and 5-fluorouracil (ECF) or cisplatin/5-fluorouracil in stage ≥II disease. Both experimental arms were demonstrated to improve 5-year survival rates by 13% and 14%, respectively, over surgery alone, although only 42% of the patients received the full perioperative courses according to protocol. The benefit seemed to be more pronounced in younger patients with a good performance status.
Nevertheless, the 5 year survival rate of clearly less than 50% in the best arm of the MAGIC trial remains unsatisfactory, and warrants the search for further potent drugs with cytotoxic or molecularly targeted mechanism of action, such as taxanes, platin alternatives or monoclonal antibodies.

### 1.1.3 Novel cytostatic agents in the treatment of advanced gastric cancer

#### 1.1.3.1 Oxaliplatin as alternative to cisplatin

Oxaliplatin is a third-generation platinum complex with a mechanism of action, spectrum of activity and toxicity profile quite different from cisplatin. In pre-clinical experiments it showed synergy with 5-FU, and this combination is a current standard in colorectal cancer. Several phase II trials proved the efficacy of oxaliplatin combinations in advanced gastric cancer, with promising response rates between 45% and 55% in the first-line studies. The so-called FLO combination, consisting of a 24h continuous infusion of 2600 mg/m² 5-FU (i.e. without bolus component), 500 mg/m² folinic acid and 85 mg/m² oxaliplatin, repeated every two weeks, in previously untreated metastatic stomach cancer achieved a response rate of 43%, with a median progression-free survival of 5.6 months and overall survival of 9.6 months. This predominantly out-patient regimen showed an efficacy which is comparable to the FOLFOX6 combination. However, the toxicity was distinctly lower with FLO, especially with respect to myelosuppression, stomatitis and peripheral neuropathy. In a subsequent phase III trial of the same group FLO was compared to the FLP regimen (5-FU, leucovorin and cisplatin), confirming the favourable profile. Anemia, fatigue, nausea, vomiting, alopecia, and nephrotoxicity were significantly less frequent, with neuropathy only being more dominant in the oxaliplatin arm. In addition, FLO showed some tendency to improved progression-free and overall survival, especially in the elderly patient subgroup (> 65 years). This is all the more important, as the median age of males and females with gastric cancer in Germany is 70 and 75 years, respectively. These results from Germany support the findings of the UK REAL-2 study including 1000 patients, showing a retained antitumor efficacy when cisplatin is replaced by oxaliplatin in the ECF triplet combination. Overall, oxaliplatin can be considered as an equi-effective, more convenient alternative to cisplatin in the treatment of gastric cancer. Due to its low hematotoxicity the FLO regimen seems to be predestined as a backbone for further treatment intensification.

#### 1.1.3.2 Taxanes as a third drug

In several phase II studies single drug docetaxel produced response rates ranging from 17 to 24% in advanced gastric cancer. In combination with cisplatin the taxane achieved response rates of 37 to 56% with survival medians of 9 to 11 months. In 2006 the results of a pivotal phase III trial (TAX 325 study) involving 457 patients were published, on the combination of docetaxel 75 mg/m² plus cisplatin 75 mg/m² on day 1 plus 5-FU 750 mg/m²/day by continuous intravenous
infusion over 5 days every 3 weeks (TCF) compared with cisplatin 100 mg/m² on day 1 followed by 5-day infusion of 5-FU 1000 mg/m²/day every 4 weeks (CF)\textsuperscript{19}. Median TTP was longer with TCF (5.6 mo) compared to CF (3.7 mo; hazard ratio 0.68, \(p=0.0004\)). With a median follow-up of 23 months, OS was improved with TCF with a 2-year survival rates of 18% with TCF vs 9% with CF (hazard ratio 0.77, \(p=0.0201\)). The response rate with TCF (37%) was superior to CF (25%; \(p=0.011\)). The safety profile was as expected. The most common grade \(\geq\) 3 non-hematological adverse events included diarrhea and stomatitis (20%/8% and 21%/27% TCF/CF). Neutropenia was more frequent in TCF with febrile neutropenia/neutropenic infection in 30% of patients. This rate was decreased (12% of patients) when G-CSF was given as secondary prophylaxis. Septic deaths occurred in 3% of patients in both arms. In addition, quality of life (EORTC QLQ C30) and performance status were maintained for a longer period in the TCF arm\textsuperscript{20}. Thus, adding docetaxel to standard CF offers a new therapeutic option in this setting. However, the DCF regimen often leads to severe myelosuppression and subsequent complications, which may preclude this approach in elderly patients (the TAX325 patients had a comparatively low median age of 55 years with only few patients beyond an age of 65). In the majority of gastric cancer patients DCF may therefore be inappropriate as palliative treatment\textsuperscript{14,15,21}.

1.1.3.3 The FLOT combination

In a small phase I/II study Dima et al.\textsuperscript{22} investigated the combination of docetaxel 50 mg/m² combined with oxaliplatin 85 mg/m², leucovorin 400 mg/m², 5-FU 400 mg/m² as bolus and 5-FU 3000 mg/m² as 48h infusion in gastric cancer. Efficacy results were promising with a response in 7 out of 16 patients. No dose-limiting toxicity and no grade 3/4 non-hematological toxicity was observed, with grade 2/3 leukopenia occurring in only 3/16. Accordingly, no maximum tolerable dose was defined. In an AIO study by Al-Batran et al.\textsuperscript{23} including 59 patients with measurable, locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction and no prior chemotherapy received a modified FOLFOX (oxaliplatin 85 mg/m², leucovorin 200 mg/m², and fluorouracil 2.6 g/m² via 24hr infusion) in combination with docetaxel 50 mg/m² on day 1 every 2 weeks (FLOT regimen). Prophylactic G-CSF was not administered. Median age was 60 (range, 29–76), median ECOG performance status was 1, and almost all patients (93%) had metastatic disease. Of 52 evaluable patients, 2 had a CR and 28 patients attained a PR, adding to an overall response rate (ORR) of 58% (51% in an ITT approach). Stable disease was observed in 12 (23%) and progressive disease in 6 (12%) patients. Four (8%) pts were not evaluable for response. NCI-CTC grade 3 or 4 hematologic toxicity included leukopenia in 15 (28%), neutropenia in 26 (48%), and anemia in 2 (4%) of evaluable patients. Febrile neutropenia was observed in 1 (2%) patient only. Other grade 3 or 4 toxicities included peripheral neuropathy in 45 (9%), nausea in 3 (6%), vomiting in 2 (4%), diarrhea in 8 (15%) and fatigue in 6 (11%) patients. No treatment related deaths were observed. These feasibility and toxicity
data compare favourably to the results reported for the DCF regimen. Therefore a randomized study on the application of this 3-drug regimen in elderly patients was initialized within the AIO (FLOT65+ trial). 143 patients were equally distributed on the FLO and FLOT arms, and received a median of 8 chemotherapy cycles. Response rate was significantly increased in the docetaxel group (49% vs. 28%, p = 0.018), as was time to treatment failure (4.4 vs. 3.8 months, p = 0.012) and progression-free survival (9.1 vs. 6.7 months, p = 0.048). Overall survival showed a trend in favour of the three-drug regimen (median 17.3 vs. 14.4 months). Although neutropenia, alopecia, nausea, and diarrhea were more frequent in the FLOT arm, there were no differences with respect to serious adverse events and treatment withdrawals/discontinuations due to toxicity. Moreover, quality of life was not compromised in this elderly patient group (data on file).

1.2 TRASTUZUMAB (HERCEPTIN®) AND ITS HER2 TARGET

1.2.1 The HER2 target in oncology

HER1, HER2, HER3, and HER4 (also called epidermal growth factor receptors ErbB-1, ErbB-2, ErB-3, and ErB-4, respectively) are transmembrane tyrosine kinase receptors with partial homology that normally regulate cell growth and survival, as well as adhesion, migration, differentiation, and other cellular responses. Each of these receptors consists of an extracellular binding domain, a transmembrane lipophilic segment, and (except for HER3) a functional intracellular tyrosine kinase domain. The tyrosine kinase domains are activated by both homodimerization and heterodimerization, generally induced by ligand binding. In contrast to the extracellular domains of the three other HER receptors, the extracellular domain of HER2 can adopt a fixed conformation resembling a ligand-activated state, permitting it to dimerize in the absence of a ligand. Receptor overexpression or mutation can also induce dimerization. Once activated, the signal-transduction cascades of these receptors promote cellular proliferation and survival, through the RAS–MAPK pathway and through the phosphatidylinositol 3'-kinase–AKT–mammalian target of rapamycin (mTOR) pathway, respectively. HER2 overexpression has first been described in breast cancer, but has since been detected in a variety of other human malignant conditions.

1.2.2 HER2-targeted treatment

The monoclonal antibody trastuzumab (Herceptin®) consists of two antigen-specific sites that bind to the juxtamembrane portion of the extracellular domain of the HER2 receptor and that prevent the activation of its intracellular tyrosine kinase. The remainder of the antibody is human IgG with a conserved Fc portion. Several possible mechanisms by which trastuzumab might decrease signalling include
prevention of HER2-receptor dimerization, increased endocytotic destruction of the receptor, inhibition of shedding of the extracellular domain, and immune activation. Preclinical models suggested that trastuzumab recruits immune effector cells that are responsible for antibody-dependent cytotoxicity. The finding that animals deficient in immune-cell–activating Fc receptors (on effector cells) do not have a response to trastuzumab provides support for this hypothesis. Preoperative administration of trastuzumab has been reported to increase tumor infiltration by lymphoid cells and modulation of in vitro antibody-dependent cytotoxicity.

Based on results of a large pivotal study, trastuzumab is approved for the treatment of advanced breast cancer since the year 2000. Clinical trials on its use as adjuvant treatment, including more than 10,000 patients, gave overwhelming evidence for major efficacy in this disease setting.

1.2.3 HER2 and trastuzumab in gastric cancer

There is growing evidence that HER2 is an important biomarker and key driver of tumorigenesis also in cancer of the gastroesophageal junction or the stomach, with studies showing amplification or overexpression in 7–34% of tumors. Although reports are conflicting, some studies have suggested that HER2-positive status in gastric cancer is associated with poor outcomes and aggressive disease.

In preclinical models of gastric cancer, trastuzumab showed at least additive antitumor effects when combined with capecitabine or cisplatin, or both. In view of the high unmet medical need in gastric cancer, a HER2 positivity rate similar to breast cancer, and the good tolerability profile of trastuzumab in patients with breast cancer, investigation of trastuzumab in patients with gastric cancer was warranted.

The international Trastuzumab for Gastric Cancer (ToGA) study recruited 594 advanced gastric or gastroesophageal cancer patients in 122 centres in 24 countries between September, 2005, and December, 2008. Patients were eligible if their tumors showed overexpression of HER2 by immunohistochemistry or gene amplification by FISH. Participants were randomized to receive a chemotherapy regimen consisting of capecitabine plus cisplatin or 5-fluorouracil plus cisplatin given every 3 weeks for six cycles or chemotherapy in combination with intravenous trastuzumab at a dose of 8 mg/kg BW on day 1 of the first cycle, followed by 6 mg/kg every three weeks until disease progression, unacceptable toxicity or withdrawal of consent. The median no. of cycles of trastuzumab was 8 (i.e. patients were 24 weeks under treatment). Overall survival, as the primary endpoint, was prolonged to a median of 13.8 months in those assigned to the antibody compared with 11.1 months in those assigned to chemotherapy alone (hazard ratio [HR]: 0.74, 95% CI 0.60 - 0.91; p = 0.0046).
The benefit was even larger, when a post-hoc subgroup analysis focusing on patients with high expression (immunohistochemistry 2+ and FISH positive or immunohistochemistry 3+; n=446) was performed. The HR for patients whose tumors had high HER2 expression was 0.65 (95% CI 0.51 – 0.83) and median overall survival was 16.0 months (95% CI 15–19) in those assigned to trastuzumab plus chemotherapy compared with 11.8 months (10–13) in those assigned to chemotherapy alone. There was evidence of a significant interaction test (p=0.036) between treatment and the two HER2 intensity subgroups (high HER2 expression vs. low HER2 expression).

Median progression-free survival was likewise significantly prolonged from a median of 5.5 months to 6.7 months (HR = 0.71; p = 0.0002), as overall tumor response rate was increased from 35% to 47%. The adverse event profile was similar between the groups, with no difference in the overall rate of adverse events (all NCI CTC grades or grade 3 or 4). Nausea, neutropenia, vomiting, and anorexia were the most frequently reported adverse events. Patients assigned to trastuzumab plus chemotherapy had slightly higher overall rates of diarrhoea, stomatitis, anaemia, thrombocytopenia, fatigue, chills, weight loss, pyrexia, mucosal inflammation, and nasopharyngitis than did patients assigned to chemotherapy alone. There was no difference between groups in frequency of grade 3 or 4 adverse events apart from diarrhoea (9% vs. 4%). Cardiac events occurred with a frequency of 6% in both study groups. 6% suffered from severe infusion-related symptoms in the trastuzumab group, but none of these reactions were fatal. No increase in dose modifications or interruptions was reported with trastuzumab.

Based on this pivotal trial, trastuzumab is approved for the combination treatment of advanced, HER2 positive (defined as: immunohistochemistry 2+ and FISH positive or immunohistochemistry 3+) gastric cancer since February 2010.

1.2.4 Duration of trastuzumab treatment

In breast cancer there is a plethora of data in the neoadjuvant/adjuvant setting where trastuzumab was given in a protracted manner after the backbone CT had ceased, altogether for about 1 year at least, showing consistent beneficial effects for overall survival and DFS with HRs between 0.48 and 0.77. In 5 of 6 large trials these differences reached statistical significance (see review by Costa et al.37). However, in the FinHER trial, a smaller (N=231 exposed patients) short term trial applying 9 1-week cycles of adjuvant trastuzumab treatment38,39, a statistically non-significant trend for improved overall survival and an improvement in distant DFS with a HR of 0.65 (p=0.12; or 0.57 [p=0.047] after adjustment for axillary nodal metastases according to a later analysis39).

However, in the longer term schemes overall adverse events (e.g. 40) as well as cardiac events were elevated in the trastuzumab arms but were mostly mild to moderate in intensity37. Shorter durations of application apparently do not have a marked effect on AE or cardiac event rates. In the FIN-HER trial (9 weeks)38 no
difference was noted regarding any grade 3/4 toxicity as well as cardiac events. In the ToGA-study in gastric cancer (median duration 24 weeks) a mixed picture emerged: Neither for any grade 3/4 toxicity nor for the overall cardiac adverse event rate and grade 3/4 cardiac adverse events a difference was noted, whereas cardiac dysfunction (defined as ≥10% drop in LVEF to an absolute value <50%) was elevated under trastuzumab (5% vs. 1%)\textsuperscript{36}.

1.3 **Rationale of the Study**

The current prognosis of patients with locoregionally spread cancer of the gastroesophageal junction or the stomach is still comparatively poor, with clearly less than half of the patients cured despite perioperative chemotherapy using cisplatin and 5-FU. Thus, the development of new regimens, including agents with novel mechanisms of action, is warranted.

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. There is a strong suggestion that the antibody may show a beneficial effect in locoregionally advanced disease as well. A similar treatment development has been successfully carried out for trastuzumab in breast 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\textsuperscript{23}. The favourable toxicity in comparison to other established chemotherapy triplets led to a good acceptance even in elderly patients. 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 the 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.

Concerning the primary endpoint, pCR rate, 4 bi-weekly trastuzumab administrations are considered optimal in this context. Nevertheless, regarding the more patient relevant secondary outcomes DFS or OS a treatment of only 8 weeks appeared to be poorly justifiable in comparison to the available evidence deriving from several studies conducted in patients with early HER2-positive breast cancer, where a 12-months treatment with trastuzumab is regarded standard therapy with proven benefit and tolerable levels of toxicities. 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.

Simultaneously, the probability of an elevation of severe cardiac events appears to be minimal based on the available data from BC and GC patients.

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 (cf appendix 8).

2 STUDY OBJECTIVES

2.1 PRIMARY ENDPOINT

Primary endpoint of the study is to estimate the efficacy of the trastuzumab/FLOT combination consisting of 5-FU/leucovorin, oxaliplatin, docetaxel and the antibody in locoregional cancer of the stomach or gastroesophageal junction, based on 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.

2.2 SECONDARY OBJECTIVES AND ENDPOINTS

Secondary endpoints are:

- 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 are:

- Evaluation of prognostic and predictive markers (cf. appendix 8)
- To describe perioperative morbidity and mortality
- To describe safety and tolerability of the trastuzumab/FLOT regimen

3 STUDY DESIGN

3.1 TYPE OF STUDY

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

3.2 PATIENT NUMBER

53 patients evaluable for the primary endpoint are required (cf. 7.2.2 for details).

3.3 TIME SCHEDULE

Start of recruitment: Oct. 2011
First Patient In: Nov. 2011
(signed informed consent of 1st patient)
Last Patient In: Oct. 2013
(signed informed consent of last patient)
End of Treatment: Sep. 2014
(last follow-up visit of last patient)

3.4 NUMBER OF CENTERS

The study will be conducted in approximately 30 study centers.

4 PATIENT SELECTION

4.1 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.

• ECOG ≤ 2

• Exclusion of distant metastasis by CT of thorax and abdomen, bone scan or MRI (if osseous lesions are suspected due to clinical signs)

• Laparoscopic exclusion of peritoneal carcinomatosis, if suspected clinically

• Adequate haematological, hepatic and renal function parameters:
  - Leukocytes ≥ 3000/mm³, platelets ≥ 100,000/mm³
  - Serum creatinine ≤ 1.5 x upper limit of normal, or GFR > 40 ml/min
  - Bilirubin ≤ 1.5 x upper limit of normal, AST and ALT ≤ 3.5 x upper limit of normal, alkaline phosphatase ≤ 6 x upper limit of normal

• Normal cardiac ejection fraction, as assessed by echocardiography

• Written patient consent form

4.2 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
5 TREATMENT

5.1 OVERVIEW

Fig. 1

Pre-operative Treatment (4 cycles)
- Trastuzumab 4 mg/kg BW*, d1
- followed by: Docetaxel 50 mg/m², 2h, d1
- followed by: Oxaliplatin 85 mg/m², 2h, d1
- followed by: Folinic acid 200 mg/m², 1h, d1
- followed by: 5-FU 2600 mg/m² (24h infusion), d1
  (=1 cycle)
Start of next cycle on day 15

Clin. Restaging
3 weeks

Surgery

Post-operative Treatment (4 cycles)**
- Trastuzumab 4 mg/kg BW*, d1
- followed by: Docetaxel 50 mg/m², 2h, d1
- followed by: Oxaliplatin 85 mg/m², 2h, d1
- followed by: Folinic acid 200 mg/m², 1h, d1
- followed by: 5-FU 2600 mg/m² (24h infusion), d1
  (=1 cycle)
Start of next cycle on day 15

Follow-up
Endpoints:
- RFS
- OS
- Prognostic factors
- pCR as surrogate marker

Post-operative Treatment
Trastuzumab Monotherapy (9 cycles)
- Trastuzumab 6 mg/kg BW, 1h, d1
  (=1 cycle)
Start of next cycle on day 22

Endpoints:
pCR rate (primary)
R0 rate

* 6 mg/kg loading dose at first administration

** Patients not tolerating post-op chemotherapy may switch to trastuzumab monotherapy 6mg/kg BW every 3 weeks. Not administered post-op. chemotherapy cycles will be replaced by additional trastuzumab monotherapy cycles according to section 5.2.3. Patients with clear signs of progression during/after pre-operative therapy go off protocol treatment
5.2 Treatment Scheme

5.2.1 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

5.2.2 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 day 1 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).

5.2.3 Additional trastuzumab monotherapy

Patients, who prove to be ineligible for post-operative chemotherapy, may switch to trastuzumab monotherapy (6 mg/kg BW every 3 weeks). Not administered post-op. chemotherapy cycles will be replaced by additional trastuzumab monotherapy cycles according to following schedule.

<table>
<thead>
<tr>
<th>Post-op. chemotherapy + trastuzumab cycles given</th>
<th>Additional cycles trastuzumab monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 cycles given</td>
<td>3 cycles 6 mg/kg BW (8 mg/kg BW loading dose in cycle 1 of 3)</td>
</tr>
<tr>
<td>1 cycle given</td>
<td>2 cycles 6 mg/kg BW</td>
</tr>
<tr>
<td>2 cycles given</td>
<td>1 cycle 6 mg/kg BW</td>
</tr>
<tr>
<td>3 cycles given</td>
<td>1 cycle 6 mg/kg BW</td>
</tr>
</tbody>
</table>
5.3 **STUDY MEDICATION**

5.3.1 **Distribution and accountability of study medication**

The investigational study drug in this trial is trastuzumab only. As docetaxel, oxaliplatin and 5-fluorouracil/leucovorin are generally available and established for the routine treatment of gastric cancer, they are considered as chemotherapy backbone medication. Thus, the latter drugs will be prescribed by the treating physician, as this prescription is within the framework of standard usage. SUSAR assessment is focused on the investigational drug only (cf. section 6.6.2).

The supply with trastuzumab is supported by Roche Pharma AG as a research grant. It will be delivered to the participating centers free of charge.

The investigator or a pharmacist or other appropriate individual, who is designated by the local principal investigator, should maintain records of the trastuzumab inventory at the site, the use for each subject, and the delivery, storage and destruction. Investigators should maintain records that adequately document that subjects were provided the doses specified in the protocol and reconcile all the investigational product received from the sponsor.

The investigator should ensure that the investigational product is used only in accordance with the protocol.

5.3.2 **General information on the study medication**

The relevant information on the drug characteristics, storage, application, mode of action and adverse reactions is included in the Summary of Product Characteristics (SmPC, "Fachinformation", appendix 4) for the antibody and the chemotherapy backbone drugs.

5.3.3 **Docetaxel**

5.3.3.1 **Formulation**

Docetaxel (trade name: TAXOTERE®) is available as a clear yellow to brownish-yellow sterile, non-pyrogenic viscous solution, in single-dose vials containing 80 mg (2.0 ml) docetaxel (anhydrous). Each ml contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

5.3.3.2 **Dispensing**

For preparation of the Taxotere® solution, see the Fachinformation (App. 6). Taxotere® will be administered to the patient as a two hour i.v. infusion.

Pre-medication with corticosteroids is mandatory (refer to section 5.7).
5.3.3.3 Handling precautions

Taxotere® is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Taxotere® solutions. The use of gloves is recommended. If Taxotere® concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If Taxotere® concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Concentrate and solvent have to be stored between 2-25°C and retained in the original package to protect from bright light. Freezing does not adversely affect the product.
5.3.3.4 Possible adverse effects

Neutropenia, thrombocytopenia, hypersensitivity reactions, fluid retention, nail disorders, alopecia, stomatitis, nausea/vomiting, neurosensory and neuromotoric disturbances, arrhythmia, anorexia, myalgia. For further information see the Fachinformation (App. 6).

5.3.4 Oxaliplatin

5.3.4.1 Formulation

Oxaliplatin (trade name: e.g. Eloxatin®) is presented as a clear, colourless solution packaged in glass vials of 20mL with oxaliplatin 100mg of active compound to be diluted for infusion.

5.3.4.2 Dispensing

Oxaliplatin will be administered in 500 mL of 5% glucose solution to the patient as a two hour i.v. infusion. Oxaliplatin should always be administered before 5-FU. For further information see the Fachinformation (App. 6).

5.3.4.3 Handling precautions

Oxaliplatin is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing oxaliplatin solutions. The use of gloves is recommended.

If oxaliplatin concentrate, reconstituted solution or infusion solution should come into contact with skin wash immediately and thoroughly with water. If oxaliplatin concentrate, premix solution or infusion solution should come into contact with mucous membranes wash immediately and thoroughly with water.

Do not combine with alkaline medications or media that cause oxaliplatin to degrade. Do not administer other agents simultaneously by the same line. Flush line after oxaliplatin administration before using the line to administer other agents. Do not use preparation or administration needles or intravenous sets containing aluminium components, as there is a risk of oxaliplatin degradation.

5.3.4.4 Possible adverse effects

Nausea/vomiting, diarrhea, leukopenia, thrombocytopenia, anemia, increase of liver enzymes, alopecia, peripheral neurotoxicity. Please refer to the SmPC ("Fachinformation") in App. 4 for further details.
5.3.5 5-Fluorouracil / leucovorin

Folinic acid and 5-FU are administered as described in section 5.1, according to the respective package inserts and local routine. Major adverse effects of 5-FU are: Nausea/vomiting, diarrhea, mucositis, hand-foot-syndrome, cardiac function disturbances, skin alterations, alopecia, hematotoxicity.

5.3.6 Trastuzumab

5.3.6.1 Distribution and accountability

Trastuzumab will be delivered free of charge by Roche Pharma AG through the Customer Center (Roche Pharma AG, P.O. Box: 1270, D-79630 Grenzach-Wyhlen). In order to be able to account for the distribution and application of the drug, a detailed record has to be kept by the investigator.

5.3.6.2 Packaging and formulation

Each vial of trastuzumab contains 150 mg of the humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures. Trastuzumab is a white to pale yellow lyophilised powder for concentrate for solution for infusion.

5.3.6.3 Labelling and storage

Each vial of trastuzumab will be labelled in accordance with current ICH GCP and specific national requirements.

Trastuzumab must be stored in a secured area upon receipt, in a refrigerator at 2 - 8°C. After reconstitution with water for injections the reconstituted solution is physically and chemically stable for 48 hours at 2°C – 8°C. Any remaining reconstituted solution should be discarded.

Solutions of trastuzumab for infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/ml (0.9%) solution for injection for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and trastuzumab infusion solution should be used immediately. The product is not intended to be stored after reconstitution and dilution unless this has taken place under controlled and validated aseptic conditions.
5.3.6.4 Preparation and administration

Appropriate aseptic technique should be used. Each vial of trastuzumab is reconstituted with 7.2 ml of water for injections. Use of other reconstitution solvents should be avoided. This yields a 7.4 ml solution for single-dose use, containing approximately 21 mg/ml trastuzumab, at a pH of approximately 6.0. A volume overage of 4 % ensures that the labelled dose of 150 mg can be withdrawn from each vial.

Trastuzumab should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of trastuzumab that can be withdrawn from the vial. The reconstituted solution should not be frozen.

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 ml of 0.9 % sodium chloride solution. Do not use with glucose-containing solutions.

5.3.6.5 Possible adverse effects

Amongst the most serious and/or common adverse reactions reported in trastuzumab usage to date are cardiotoxicity, infusion-related reactions, hematotoxicity (in particular neutropenia) and pulmonary adverse events.

Cardiotoxicity

Cardiotoxicity (heart failure), NYHA II - IV is a common adverse reaction associated with the use of trastuzumab and has been associated with a fatal outcome.

The safety of continuation or resumption of trastuzumab in patients who experience cardiotoxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal trials improved with standard medical treatment. This included diuretics, cardiac glycosides, beta-blockers and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on therapy with trastuzumab without additional clinical cardiac events.

Infusion reactions, allergic-like reactions and hypersensitivity

Serious adverse reactions to trastuzumab infusion that have been reported infrequently include dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema. The majority of these events occur during or within 2,5 hours upon start of the first infusion. Should an infusion reaction occur the infusion needs to be discontinued or the rate of infusion decreased and the patient monitored until resolution of all observed symptoms. The majority of patients experienced resolution of symptoms and subsequently received
further infusions of trastuzumab. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions may be associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

**Hematotoxicity**

Febrile neutropenia occurred very commonly. Commonly occurring adverse reactions included anaemia, leukopenia, and thrombocytopenia. The frequency of occurrence of hypoprothrombinemia is not known.

**Pulmonary events**

Severe pulmonary adverse reactions occur in association with the use of trastuzumab and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency.

Cf. the SmPC (App. 4) for further details.

5.4 **MODIFICATIONS OF THERAPY AND DOSAGE**

5.4.1 **General remarks**

Toxicity will be graded according to NCI CTCAE, version 4.0 (appendix 3); the therapy modifications described below are applied according to this severity grading.

Toxicities of severity grade 1 only will not lead to any dose reduction or cycle delay. The same holds for adverse reactions without any potential of serious or life-threatening complications according to the judgment of the physician (e.g. alopecia). Presumably, severe overlapping toxicity between chemotherapy and antibody will not occur. Thus, in case of toxicity requiring treatment modification, this alteration should reflect the causal relationship of the respective drug(s). E.g., if the toxicity is unequivocally caused by only one drug, a dosage modification of the other drugs is not required.

If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

In case of a necessary dose reduction the lower dose level will be applied throughout the rest of the therapy without re-escalation, if not stated otherwise. If toxicity requires a cycle delay of more than 3 weeks the patient is taken off protocol.
treatment except for the first 4 post-operative cycles where the patient may switch to trastuzumab monotherapy (6 mg/kg BW every 3 weeks). Not administered post-op. chemotherapy cycles will be replaced by additional trastuzumab monotherapy cycles according to section 5.2.3.

In case of acute allergic reactions of grade 3 or 4, the respective agent should be discontinued permanently; in case of grade 1 or 2, it is up to the physician to continue treatment without dose modification, if this is in the best interest of the patient.

Each dose modification or treatment delay has to be documented in the CRF, including the respective reason.

5.4.2 Modifications of chemotherapy

5.4.2.1 Dose adjustment/delay in case of hematotoxicity

In case of myelosuppression persisting on the planned day 1 of the next cycle, the following measures should be taken:

- WBC < 3,000/µL  Therapy delay for at least 1 week
- Platelets < 100,000/µL  Differential blood counts at least weekly

In case of febrile neutropenia (in spite of secondary prophylaxis hematological growth factors, cf. section 5.7.5) or thrombopenia with bleeding, oxaliplatin and docetaxel will be reduced to 75% of the initial dose. If these toxicities are observed again, a second reduction to 50% of the full dose has to be performed. If the toxicity re-occurs, the chemotherapy will be continued with 5-FU only.

5.4.2.2 Dose adjustment in case of diarrhea / mucositis

In case of diarrhea and/or mucositis ≥ grade 3, 5-FU and docetaxel have to be reduced to 75% of the initial dose. If these toxicities are observed again, a second reduction to 50% of the full dose has to be performed. If the toxicity re-occurs, the chemotherapy will be stopped permanently.

5.4.2.3 Dose adjustment in case of oxaliplatin neurotoxicity

Peripheral neurotoxicity will lead to the following dose adaptations (Tab. 1):
Tab. 1  
**Oxaliplatin dose modification in case of neurotoxicity**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>≤ 7 days</th>
<th>&gt;7 and &lt;14 days</th>
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<td>no change</td>
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<td>no change</td>
<td>no change</td>
<td>reduction to 75%</td>
</tr>
<tr>
<td>Paresthesia with pain</td>
<td>no change</td>
<td>reduction to 75%</td>
<td>stop of oxaliplatin; docetaxel and 5-FU continued</td>
</tr>
<tr>
<td>Paresthesia with functional impairment</td>
<td>no change</td>
<td>reduction to 50%</td>
<td>stop of oxaliplatin; docetaxel and 5-FU continued</td>
</tr>
</tbody>
</table>

Termination of oxaliplatin should not be reintroduced if once stopped.

5.4.2.4 **Dose adjustment in case of nephrotoxicity**

If creatinine clearance drop to the range below 40 mL/min, but > 30 mL/min, hyperhydration for 48 hours will be performed with a subsequent reassessment of the clearance. In case of persisting low kidney function in the range mentioned above oxaliplatin will be reduced to 75% of the initial dose. In case of creatinine clearance below 30 mL/min in the pre-operative treatment phase the chemotherapy treatment terminated and the patient goes off protocol treatment. In case of creatinine clearance below 30 mL/min in the post-operative treatment phase the chemotherapy treatment is terminated and the patient may switch to trastuzumab monotherapy (6 mg/kg BW every 3 weeks). Not administered post-op. chemotherapy cycles will be replaced by additional trastuzumab monotherapy cycles according to section 5.2.3.

5.4.2.5 **Dose adjustment in case of other toxicities**

If other toxicities of NCI CTC grade 3 to 4 occur, a dose adjustment of the cytostatic drug most probably responsible for the event should be reduced. Consultation of the study coordinator is recommended.

5.4.3 **Modifications of trastuzumab treatment**

5.4.3.1 **Interruption of trastuzumab infusion**

Subjects who experience any serious infusion reaction during trastuzumab administration will have the infusion discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms.
Continuation of dosing and trastuzumab re-treatment will be based on the severity and resolution of the event and will be at the discretion of the investigator.

Suspected infusion reactions should be reported as an adverse event. All subjects who experience such an event will be followed up for safety.

5.4.3.2 Trastuzumab dosage adjustments

No trastuzumab dose reductions are planned.

5.5 Precondition for start of a new treatment cycle

The following requirements have to be met, before a new treatment cycle may be administered:

- No hematotoxicity of grade ≥2 (i.e. WBC > 3000/µL, platelets > 75,000/µL)
- No stomatitis, diarrhea, hand-foot syndrome or other non-hematological toxicity (except for alopecia, nausea and vomiting) of grade ≥2 (for neurotoxicity cf. section 5.4.2.3, for nephrotoxicity cf. section 5.4.2.4)
- No ongoing requirement for anti-diarrheic treatment
- Bilirubin ≤ 3.0 x UNL
- Transaminases ≤ 3.5 x UNL
- No persisting cardiac toxicity
- No treatment delay of more than 3 weeks (in case of chemo therapy treatment delay of more than 3 weeks in post operative phase patients are not withdrawn from study treatment and may switch to trastuzumab monotherapy (6 mg/kg BW every 3 weeks). Not administered post-op. chemotherapy cycles will be replaced by additional trastuzumab monotherapy cycles according to section 5.2.3.

In case of treatment delay in the combination therapy both FLOT and trastuzumab have to be delayed in parallel.

5.6 Compliance

All antineoplastic drugs are administered i.v., with the date and amount recorded in the CRF.
5.7 **CONCOMITANT AND SUPPORTIVE TREATMENT**

5.7.1 **General aspects**

In general, the patients should continue to take their previous therapies according to the recommendations of the responsible physician. The following concomitant therapies will not be allowed:

- any other antineoplastic treatment
- other investigational therapies

All concomitant medication has to be recorded. Additionally, any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded.

Supportive care for treatment-related symptoms will be offered as needed to all patients in this study.

5.7.2 **Pre-treatment**

All patients must receive 8 mg of dexamethasone p.o. on the evening before start of each chemotherapy cycle (d0), to prevent allergic reactions and/or severe fluid retention.

5.7.3 **Treatment of nausea/vomiting**

For acute nausea and vomiting (ANV), a 5-HT3 antagonist with corticosteroids prior to infusion is considered standard premedication. For patients with individual risk factors for ANV the addition of aprepitant should be considered. Aprepitant is licensed for the prophylactic treatment of ANV caused by moderate emetogenic therapies (such as the FLOT regimen). For delayed nausea and vomiting, dexamethasone or the addition of aprepitant to the next treatment cycle are first options; metoclopramide, alizapride and prochlorperazine may be also used. However, deviating center specific treatment options are allowed.

5.7.4 **Treatment of diarrhea**

Diarrhea and/or abdominal cramping should be managed according to standard institutional practice, or according to the following recommendations:

A prophylactic treatment is not recommended. As soon as signs of diarrhea occur, the patient should immediately consult his physician and start with the intake of loperamide: 2 capsules (4 mg), thereafter 1 capsule (2 mg) every two hours, for at least 12 hours and for at least 12 hours after the last observation of liquid stool. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to
discuss any laxative use. Sufficient oral rehydration has to be administered during
the whole diarrhea episode.
If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting must be hospitalized for intravenous hydration and correction of electrolyte imbalances. In case of persisting severe diarrhea despite loperamide treatment, this drug should be replaced by another antidiarrheic therapy (e.g. octreotide).

5.7.5 Prevention and treatment of neutropenia

Hematopoietic growth factors (i.e., G-CSF or pegylated G-CSF) may be used according to institutional or other specific guidelines (e.g. EORTC) as secondary prophylaxis, i.e. to treat febrile neutropenia or neutropenia with infection, or after a cycle delay of > 3 days due to WBC toxicity. Use of any supplementary growth factor must be documented in the patient record. Growth factors must be discontinued at least 48 hours prior to initiation of the next cycle of chemotherapy.

Prophylactic treatment with antibiotics is not recommended.

5.8 SURGICAL PROCEDURES

5.8.1 General aspects

The resection should be undertaken three weeks after day 1 of the last neoadjuvant cycle. The extent of the surgical resection and lymphadenectomy should be standardized according to the recommendations in sections 5.8.2 to 5.8.6 (however, surgery is not considered to be part of the experimental study treatment). Total gastrectomy with D2 lymphadenectomy (compartments I and II) is standard therapy for tumors of the gastric corpus. In patients with carcinoma of the proximal gastric third or carcinoma of the cardia, an additional transhiatal resection of the distal oesophagus. A pancreas preserving splenectomy with a left retroperitoneal lymphadenectomy will be performed in case of tumors located in the upper third and evidence for lymph node metastasis along the splenic artery. In patients with carcinoma of the gastric antrum the D2-lymphadenectomy will be extended to the hepatoduodenal ligament and the right retroperitoneum. A recommended number of at least 25 lymph nodes should be removed with a D2 lymphadenectomy. This allows a reliable assessment of the N-category by the pathologist. The minimum number of lymph nodes dissected is n=16.
Tumor specimen and lymph nodes specimen will be sent to the pathology department from the operating theatre. The specimen of the lymph nodes will be sent in two different parts. The separation between compartment I and compartment II is done by the operating surgeon in the operation theatre. All the borderline lymph nodes have to be marked with a suture. If necessary, additional topographic explanation should be added to the specimen.

Any extension of the procedure for the sake of a complete tumor removal is allowed but should be recorded.

5.8.2 Technique of esophagectomy with lymph node dissection in AEG type I tumors

The radical resection of a distal esophagus carcinoma AEG type I should be performed as a transthoracic en-bloc esophagectomy with radical dissection of mediastinal lymph nodes, abdominal lymphadenectomy (2-field LAD) and reconstruction with high intrathoracic, or (if necessary) cervical anastomosis after gastric pull-up or colonic interposition. The oral resection distance from the tumor should be 5 cm in situ and tumor-free resection margins should be verified by intraoperative rapid section diagnosis.

5.8.3 Technique of total gastrectomy with D2-lymphadenectomy for carcinoma of the gastric corpus (middle gastric third)

The lymphadenectomy is performed en-bloc with total gastrectomy. The procedure is started with an isolation of the distal oesophagus. The greater omentum is then dissected from the transverse colon and the lesser sac is opened. The right colonic flexure is mobilized and a Kocher manoeuvre is performed. The right gastroepiploic vein is ligated and transected at its base at superior mesenteric vein. The right gastroepiploic artery is cut at its origin from the gastroduodenal artery. The duodenum is then transected and closed about 2 cm distal to the pylorus using a stapler.

The lymphadenectomy is started at the gastroduodenal artery and continued towards the common hepatica artery. At this point the dissection of the lymph nodes is directed to the hepatoduodenal ligament up to the right gastric artery. The latter is ligated and cut at its origin. The lymphadenectomy is then performed medially along the common hepatica artery to the celiac axis. The left gastric vein is ligated and cut. The left gastric artery is dissected up to the celiac axis and transected. In case of a significant left hepatic artery originating from the left gastric artery, the latter is
transected peripheral to the origin of the left hepatic artery. The lymph node dissection is then continued orally to the diaphragmatic crura. The lymphadenectomy is performed towards the left along the splenic artery to the splenic hilum. This concludes the lymphadenectomy of the compartment II. A splenectomy or left sided pancreatic resection should be avoided. The lymph nodes of the compartment 1 (i.e. the perigastric nodes) are removed together with the stomach when resecting the lesser and greater omentum.

5.8.4 Technique of transhiatally extended total gastrectomy with extended D2-lymphadenectomy for carcinoma of the cardia or subcardial region (oral gastric third)

In order to ensure an adequate luminal safety margin for these tumor types a transhiatal resection of the distal oesophagus is performed in addition to total gastrectomy. The lymphadenectomy is extended to the left retroperitoneum by performing a pancreas preserving splenectomy with lymph node dissection to the left renal vessels. To achieve this, the splenic artery is ligated and cut immediately left to the aorta, the vein is ligated close to the splenic hilus. The vessels and associated lymph nodes are then dissected from the pancreas and removed en bloc together with the spleen and the gastrectomy specimen.

5.8.5 Technique of total gastrectomy with extended D2-lymphadenectomy for carcinoma of the gastric antrum (distal gastric third)

In patients with tumors of the distal gastric third, a lymphadenectomy of the hepatoduodenal ligament and retroduodenal region is performed in addition to a total gastrectomy and D2-lymphadenectomy. This requires an extensive mobilisation of the duodenum and posterior wall of the portal vein. The lymph nodes in this region can be pushed through the gastroepiploic foramen by the surgeon's finger after dissection from the posterior aspect of the pancreatic head. This lymphatic tissue can then be removed en bloc with the specimen. In addition, the lymph nodes in the right retroperitoneal paracaval and paraaortic region are removed.
5.8.6 **Reconstruction**

The reconstruction after total or extended gastrectomy with D2 or extended D2 lymphadenectomy is performed according to the local standards.

5.8.7 **Instructions for the preparation of resected material by the pathologist**

With respect to the study’s primary objective the rate of complete pathological response the preparation of resected material is of particular importance. The preparation has therefore to be performed according to the valid directives.

It is critical that a paraffin embedding has to be made for each square centimeter of the area suspected to be part of the tumor and the preparation of lymph nodes has to be complete. It is not sufficient to prepare only a few enlarged lymph nodes. In case no tumor is found in the preparation the entire specimen has to be paraffin-embedded. In case of unclear findings a complete preparation has to be considered. It is also recommended to sample non-neoplastic tissue from each antrum, corpus and cardia/fundus. *All* paraffin embeddings have to be sent to the central/reference pathologist.

**The material of all patients has to be sent to the reference pathologist!**

**Reference Pathologist:**

Prof. Dr. med. Andrea Tannapfel  
Institut für Pathologie der Ruhr-Universität Bochum  
am Berufsgenossenschaftlichen Universitätsklinikum Bergmannsheil  
Bürkle de la Camp-Platz 1  
44789 Bochum  
Tel.: 0234 / 302-4800  
Fax: 0234 / 302-4809
5.9 **EMERGENCY MANAGEMENT**

In case of an emergency the coordinating investigator can be approached via the following phone/fax connection:

Prof. Dr. Ralf-Dieter Hofheinz  
Tagestherapiezentrum am ITM & III. Medizinische Klinik  
Universitätsmedizin Mannheim  
Theodor-Kutzer-Ufer 1-3  
68167 Mannheim, Germany  
Phone +49-621-383-2855 or -3258  
Fax +49-621-383-2488  
Email: ralf.hofheinz@umm.de

Serious adverse events or reactions (cf. section 6.6.2 and 6.6.3), observed during the conduct of the study, have to be reported to the sponsor representative (CRO) within one working day via fax:

**ClinAssess**  
Birkenbergstr. 82  
51379 Leverkusen  
Fax: +49 (0) 2171 / 36 336 55  
Tel. +49 (0) 2171 / 36 336 0  
info@clinassess.de

A specific SAE form has to be filled.

5.10 **ENROLMENT**

Subjects fulfilling all in- / exclusion criteria, having provided written informed consent on the approved informed consent form are eligible for participation in the study.

Notification of enrolment is performed centrally by fax at

**ClinAssess**  
Birkenbergstr. 82  
51379 Leverkusen  
Fax: +49 (0) 2171 / 36 336 55  
Tel. +49 (0) 2171 / 36 336 0  
info@clinassess.de
using the recruitment form. The coordinating center will return the fax assigning the unique patient identification number for the trial.

5.11 **Premature withdrawal of an individual subject**

Patients will be removed from protocol treatment for the following reasons:

- disease progression / relapse during treatment
- occurrence of unacceptable toxicity i.e. continued decrease in left ventricular function, LVEF of 10 percentage points from its initial value and falls below 50% for 3 weeks, occurrence of clinically significant heart failure
- treatment delay more than three weeks
- administration of any other anti-neoplastic medication or any other experimental drug
- consent withdrawn
- investigator decision in the best interest of the patient
- pregnancy or insufficient contraception
- loss to follow-up
- death

The time point of and reason for removal of a patient must be documented on the case report form. The investigator will attempt to complete all discharge procedures at the time a patient is discontinued from study treatment and to record further follow-up data, if required.

5.12 **Premature study termination by the sponsor, the coordinating investigator, the competent authority and the ethics committee**

At any time, the sponsor and/or coordinating investigator of the study, the German competent authority and the ethics committee may terminate the trial participation of an individual patient, as well as the whole trial, provisionally or permanently, if this is required by stringent medical or legal reasons (including insufficient patient recruitment), especially if severe and/or frequent adverse events occur, requiring a new risk/benefit evaluation.
The continuous risk-benefit assessment of the trial, based on each and every patient during the trial is a duty of the sponsor, who will be supported by an Independent Data Monitoring Committee (IDMC) to assess the safety data in the trial.

It is specially requested that the IDMC be diligent in their monitoring of the safety data for the following criteria that could lead to discontinuation or early termination of the study:

- Medical or ethical reasons affecting the continued performance of the study:
  - General safety reason (occurrence of AEs previously unknown in respect of their nature, severity and duration, or unexpected incidence of known AEs)
  - Diarrhea of grade 3/4 in > 30% of patients
  - Febrile neutropenia in > 15% of patients
  - PNP of grade 3 in > 20% of patients
  - Major bleeding in > 10% of patients
  - Cardiac events of grade 3/4 in > 5% of patients
  - Thromboembolic events of grade 3/4 in > 10% of patients
  - Treatment-related deaths in > 5% of study population
  - Negative benefit/risk assessment due to new information
- Inappropriate recruitment of subjects
- Further external scientific evidence that this regimen might result in a suboptimal risk-benefit-assessment for the whole group of patients or for a distinct subgroup (e.g. according to clinical or molecular characteristics).

Based on their assessments of the interim safety data the IDMC members will vote for one of the following recommendations:

- Continue the study without modification;
- Suggest changes in study conduct and/or protocol;
- Stop enrolment and continue treatment;
- Stop enrolment and stop treatment.

These recommendations will be presented to the sponsor in written form.
### 6 STUDY ASSESSMENTS AND CRITERIA OF EVALUATION

#### 6.1 OVERVIEW / SCHEDULE OF STUDY ASSESSMENTS

<table>
<thead>
<tr>
<th>STUDY PARAMETERS</th>
<th>Pre-study</th>
<th>Before cycle 1-4*</th>
<th>After cycle 4</th>
<th>After surgery</th>
<th>Before cycle 5-17*</th>
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<td>X</td>
<td></td>
<td></td>
<td>X⁵</td>
</tr>
<tr>
<td>CT/MRT, abdomen</td>
<td>X³</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X¹¹</td>
</tr>
<tr>
<td>CT/MRT, thorax</td>
<td>X³</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X¹¹</td>
</tr>
<tr>
<td>Bone scan</td>
<td>X⁵</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>diagn. laparoscopy ¹²</td>
<td>X³</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HER2-neu assessment by local pathologist ¹⁴</td>
<td>X³</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tumor sample for central review</td>
<td>X³, 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

1. Within 14 days prior to the start of therapy.
2. Within 7 days prior to the start of therapy.
3. Within 28 days prior to the start of therapy.
4. In case of women with child-bearing potential.
5. As clinically indicated.
6. Every 3 months for 2 years.
7. Hb, WBC, neutrophils, platelets
8. Sodium, potassium, calcium, creatinine, GFR (acc. to MDRD formula), urea, bilirubin, GOT, GPT, LDH, alk. phosphatase.
9. Day 22 after start of last chemotherapy or trastuzumab cycle
10. Esophago-gastro-duodenoscopy; to be repeated before surgery for clinical response assessment and surgical planning. Endosonography is mandatory for TN staging.
11. Restaging tumor assessments **start 3 months after surgery**
12. In case of suspected peritoneal carcinomatosis
13. Tumor tissue from biopsy to be sent to central pathology (Stratifyer) for central review of Her2-neu status, tumor tissue from resection to be sent to central pathology (Prof. Tannapfel).
14. To be performed only after signed informed consent
15. To be performed at 1st post-operative cycle (cycle 5) thereafter echocardiography will be performed every 3 months or whenever clinically indicated

* Baseline assessments are appropriate for cycle 1, if they occurred within the required time period. Additional assessments (especially blood counts) are performed during the chemotherapy cycle (i.e. between day 2 and 14) according to center standards.

6.2 ASSESSMENTS AT RECRUITMENT

No study treatment or any other procedure (except for routine procedures) within the framework of the trial will be performed in any patient prior to receipt of written informed consent.

The following baseline assessments/procedures will be conducted or obtained within two weeks prior to start of study treatment:

- Complete medical history including dates and description of initial diagnosis of gastric cancer, pre-treatment, tumor related symptoms, relevant concurrent illnesses and relevant concomitant medication.

The following baseline assessments/procedures will be conducted or obtained within four weeks prior to start of study treatment:

- Signed written informed consent.
- Esophagus-gastro-duodenoscopy with assessment of tumor localisation length and width. In case of adenocarcinoma of the gastroesophageal junction: distance in cm from the Z line (oral and aboral).
- Endosonography for assessment of T category and lymph nodes proximate to the wall.
- Other clinical tumor assessments, if appropriate
- CT or MRT of the chest and the abdomen/pelvis
- Bone scan in case of suspected osseous metastasis
- Diagnostic laparoscopy in case of suspected peritoneal carcinomatosis
- 12 lead ECG
- Echocardiography
- HER2-neu assessment by local pathologist
- Tumor biopsy tissue for central pathology (Stratifyer) for quality assurance

The following baseline assessments will be conducted or obtained within one week prior to start of study treatment unless otherwise indicated:

- Physical examination including: weight, height, ECOG performance status
- Vital signs: blood pressure, pulse rate and oral temperature
- Current symptoms and/or residual toxicities from prior therapies should be recorded using the NCI Common Terminology Criteria for Adverse Events (appendix 3), including neurological assessment.
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count.
- Clinical chemistry: Sodium, potassium, calcium, creatinine, GFR (acc. to MDRD formula), urea, bilirubin, GOT, GPT, LDH, alk. phosphatase
- Urine or serum HCG if patient is of childbearing potential.
- Pregnancy test in case of women with child-bearing potential

The above tests and procedures are summarized in the Study Flow Sheet in section 6.1.

6.3 **ASSESSMENTS DURING AND AFTER STUDY TREATMENT**

**On day 1 of every treatment cycle (1 to 17)**

Baseline assessments are appropriate for cycle 1, if they occurred within the required time period.

- Physical examination including: weight, ECOG performance status
- Vital signs: blood pressure, pulse rate and oral temperature
- Toxicity/adverse effects according the NCI Common Terminology Criteria for Adverse Events (appendix 3), including neurological assessment.
- Clinical tumor assessments, if appropriate
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count.
- Clinical chemistry: Sodium, potassium, calcium, creatinine, GFR (acc. to MDRD formula), urea, bilirubin, GOT, GPT, LDH, alk. phosphatase
- 12 lead ECG (if clinically indicated)

Additional assessments (especially blood counts) are performed during the chemotherapy cycle (i.e. between day 2 and 14) according to center standards.

On day 1 of the first post-operative treatment cycle

- Clinical tumor assessments, if appropriate
- Echocardiography

After cycle 5 echocardiography will be performed every 3 months or whenever clinically indicated

Restaging after end of cycle 4 (2 weeks after therapy):

- Physical examination including: weight, ECOG performance status
- Vital signs: blood pressure, pulse rate and oral temperature
- Toxicity/adverse effects according the NCI Common Terminology Criteria for Adverse Events (appendix 3), including neurological assessment.
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count.
- Clinical chemistry: Sodium, potassium, calcium, creatinine, GFR (acc. to MDRD formula), urea, bilirubin, GOT, GPT, LDH, alk. phosphatase
- 12 lead ECG (if clinically indicated)
- Clinical tumor assessments, if appropriate
- Esophagus-gastro-duodenoscopy for clinical response (cf. section 6.5) and surgery planning
- CT or MRT of the chest and the abdomen/pelvis to rule out disease progression
After surgery

- Tumor tissue sample for central pathology (Prof. Tannapfel) (cf. appendix 6 for details)

At the end of treatment (day 22 after start of last iv therapy cycle)

- Physical examination including: weight, ECOG performance status
- Vital signs: blood pressure, pulse rate and oral temperature
- Toxicity/adverse effects according the NCI Common Terminology Criteria for Adverse Events (appendix 3), including neurological assessment.
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count.
- Clinical chemistry: Sodium, potassium, calcium, creatinine, GFR (acc. to MDRD formula), urea, bilirubin, GOT, GPT, LDH, alk. phosphatase
- 12 lead ECG

The above tests and procedures are summarized in the Study Flow Sheet in section 6.1.

6.4 FOLLOW-UP DOCUMENTATION

Follow-up documentation every 3 months for up to two years is mainly performed in order to assess the efficacy objectives of relapse-free and overall survival. The follow-up programme corresponds to the guidelines of the German Cancer Society. **With respect to restaging procedures, the 3-monthly schedule starts from the time point of surgery, i.e. coincides partly with the post-operative therapy.**

- Physical examination including: weight, ECOG performance status
- Vital signs: blood pressure, pulse rate and oral temperature
- Protracted toxicity/adverse effects according the NCI Common Terminology Criteria for Adverse Events (appendix 3), including neurological assessment, if clinically indicated.
- 12 lead ECG, if clinically indicated
6.5 CRITERIA FOR EFFICACY EVALUATION

6.5.1 Tumor evaluations

Non-pathologic tumor measurements are to be made using the same method (e.g. endoscopy, endosonography, MRT, CT scan) at each protocol-defined assessment. If a patient has clinical signs of progression, then tumor evaluation can take place at that time.

This tumor evaluation is performed by the oncologist/gastroenterologist in analogy to the RECIST (Response Evaluation Criteria In Solid Tumors, V. 1.1, 2009) criteria and standards (cf. appendix 1 for details). The overall objective clinical response rate is defined as the number of patients with a best response of CR or PR, divided by the total number of recruited eligible patients.

pCR as the primary endpoint of the trial is determined by reference pathology according to the regression grading system by Becker et al. (2003). The pCR rate is defined as the number of patients with a pCR finding (i.e. no tumor detected in primary tumor and lymph nodes), divided by the total number of recruited eligible patients. Further details are to be found in appendix 6 and section 7.2.

The R0 rate is defined as the number of patients with negative surgical margins and no tumor left macroscopically, divided by the total number of recruited eligible patients.

6.5.2 Perioperative morbidity and mortality

Perioperative morbidity is recorded by adverse event assessment according to section 6.6.3 and evaluated with regard to frequency, severity and duration of AEs that occur within 30 days after surgical treatment. Perioperative mortality is recorded by adverse event assessment according to section 6.6.3 and is defined as the number of deaths, within 30 days after surgery. Moreover in-hospital mortality is recorded.
6.5.3 Relapse-free survival

Relapse-free survival (RFS) will be defined as the time from enrolment to the time of disease progression or relapse or death, or to the date of last tumor assessment without any such event (censored observation).

6.5.4 Overall survival

The duration of overall survival (OS) will be determined by measuring the time interval from enrolment to the date of death or last observation (censored).

6.6 CRITERIA FOR SAFETY EVALUATION

6.6.1 Toxicity / adverse events (AE)

Adverse events (AE):

An adverse event is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.” (ICH E6:1.2).

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

Due to regulatory requirements, events occurring during pre- and post-treatment periods should also be designated as AEs. Therefore, safety surveillance - reporting of (S)AEs - commences at the time when the subject is enrolled into the study (date of signature of the informed consent) until the End of Treatment Visit has been performed or 6 months after the last dose of study treatment. Therefore events occurring in the period between the signed informed consent and beginning of the study drug administration are to be designated as AEs.
Adverse drug reaction (ADR):

All untoward and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADR). The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out or is not described as “not likely”. A serious ADR (SADR) is an ADR that meets the definition of serious (provided below).

Pre-existing diseases, when worsening during study therapy, have to be considered as adverse events. They can lead to serious adverse events, if they meet the criteria described in section 6.6.2.

All adverse events and toxicities are recorded continuously and reported in the toxicity form of the CRF (cf. section 6.6.3 for details).

6.6.2 Serious adverse events (SAE) / SUSAR

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (where the patient is at immediate risk of death)
  
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect or
- Is an important/significant medical event for any other reason

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in cases of important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (eg, emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other important/significant medical
hazard” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Hospitalization for the performing of protocol-required procedures or administration of study treatment is not classified as an SAE.

SUSARs (Suspected Unexpected Serious Adverse Reaction) represent Serious Adverse Events related to trastuzumab (=adverse reactions), considered “unexpected” with regard to the valid trastuzumab SmPC. SAEs not related to trastuzumab will not be assessed and reported as SUSARs.

6.6.3 Methods of recording and assessing adverse events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by subjects are properly captured in the subjects’ medical records. The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to study treatment; and action taken. However, due to the large number of expected adverse events due to the chemotherapy backbone (especially taxotere and oxaliplatin) and the severe underlying disease, in the CRF, the full set of information is only required for serious adverse events (see below).

All AEs must be documented with time period of onset and resolution and its maximum CTCAE (Common Terminology Criteria for Adverse Events) severity grade by cycle in the appropriate toxicity section of the CRF, together with a short judgment on causality. For serious adverse events, a SAE report form (initial or follow up) must be completed in addition (cf. end of section 6.6.4 for exemptions).

The following detailed information must be recorded for each serious adverse event:

- A description of the AE in medical terms, not as reported by the subject
- The date of onset (start date)
- The date of recovery (stop date)
- The grade as assessed by the investigator according to the definitions in CTCAE version 4.0 (cf. appendix 3):
  Grade 1 = mild
  Grade 2 = moderate
  Grade 3 = severe
  Grade 4 = life-threatening or disabling
The causal relationship to the therapy as assessed by the investigator; the decisive factor in the documentation is the temporal relation between the AE and the study drug. The following judgments of the causality to study drug or study procedures are to be used:

- **Not Related** = There is not a temporal relationship to study drug administration (too early, too late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

- **Not Likely** = There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE.

- **Possible** = There is a reasonable causal relationship between the study drug and the AE. Dechallenge information (information referring to withdrawal of drug) is lacking or unclear.

- **Probable** = There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge (withdrawal of study drug). Rechallenge is not required.

- **Certain/Definite** = There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge and recurs with rechallenge, when clinically feasible.

- **Action taken on study drug(s)** (none, medication discontinued, dose reduction, medication delayed, reduction of infusion rate).

- **Other action** (none, concomitant medication given, new or prolonged hospitalization, procedural surgery, chemotherapy delayed, chemotherapy discontinued, chemotherapy dose reduction).

- **The outcome according to the following definitions:**
  - Fatal / Date of Death
  - Resolved
  - Resolved with sequelae
  - Improved
  - Persisting
  - Worsened
  - Unknown

- In case of multiple event terms, it must be indicated which event is the leading event of the SAE, i.e. the primary medical reason for SAE reporting.

If in any one subject the same AE occurs on several occasions, then the AE in question must be documented and assessed anew each time.

Serious adverse events will be collected and recorded throughout the study period, defined as 6 Months after the last dose of study treatment. Serious adverse events occurring more than 6 Months after a patient is discontinued from the study
treatment will NOT be reported unless the investigator feels that the event may have been caused by the study drug or a protocol procedure.

6.6.4 Procedure for reporting serious adverse events

In the event of the occurrence of any clinical AE or abnormal laboratory test value that is serious (according to the definition provided in section 6.6.2) during the course of the study or the immediate post-treatment period, irrespective of the treatment received by the subject, the investigator is obliged to inform the sponsor representative (CRO) within one working day by fax:

ClinAssess  
Birkenbergstr. 82  
51379 Leverkusen  
Fax: +49 (0) 2171 / 36 336 55  
Tel. +49 (0) 2171 / 36 336 0  
info@clinassess.de

The immediate report by the investigator to the sponsor representative shall be followed by detailed, written reports using the SAE report form. The immediate and follow up reports shall identify subjects by unique code numbers assigned to the latter. SAEs will be followed until resolved or considered stable.

All SAEs have to be reported on the standard toxicity form of the CRF as well as on the specific SAE form including all required details.

The sponsor will ensure that the legal requirements for reporting adverse events to the respective federal agency ("Bundesoberbehörde", BfArM bzw. PEI [Paul-Ehrlich-Institut]) as well as to the responsible ethical committee(s), according to §13, Abs. 6, 2 and 3 of GCP-V, are fulfilled.

The sponsor is obliged to inform the participating investigators about SUSARs detected in the study (cf. section 6.6.2 for definition), according to the German regulations (§13, Abs. 2 and 3 of GCP-V).

The study sponsor is responsible for providing all serious adverse events (SAEs) to the Roche safety operations responsible within one working day according to the safety data exchange agreement (appendix 1 of the contract between the sponsor and Roche). It is possible that Roche may request follow-up information from the sponsor.

All unexpected serious adverse reactions related or possibly related to trastuzumab (SUSARs) and their follow-up reports must be reported to Roche at the same time as submission to the regulatory agency or ethical committee. A copy of any safety report submitted to the authorities or ethical committee, should be faxed to Roche (Fax no. +49/7624/14-2136), within one working day of such submission.
Exceptions: Events, which will not be regarded as SAEs:

Due to the seriousness of the disease in this study, certain conditions that qualify per definition as SAEs will be excluded from expedited reporting on a SAE report form (exemptions allowed according to §12, Abs. 4, GCP-V) if they are deemed unrelated to study drug and/or study procedure and constitute:

- An elective hospitalization and surgery for treatment of the underlying tumor disease
- An elective hospitalization to simplify treatment or study procedures
- Events, including death, that are only and unequivocally caused by progression of the underlying disease

6.6.5 Pregnancy Reporting

Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 6 months after last study treatment administration must be reported unhesitatingly to the sponsor representative (CRO). Follow-up information on the subject and her pregnancy outcome should be communicated by the Investigator to the CRO as soon as available.

Please use the pregnancy reporting form for the report and fax the report to:

ClinAssess
Birkenbergstr. 82
51379 Leverkusen
Fax: +49 (0) 2171 / 36 336 55
Tel. +49 (0) 2171 / 36 336 0
info@clinassess.de

The investigator should counsel the subject or the partner of the subject, discuss the risks of continuing the pregnancy, and possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Any pregnancy exposure has to be reported by the CRO to Roche within one working day of identification, including follow-up until the outcome is known.

6.6.6 Monitoring of subjects with adverse events

Any AE that occurs in the course of the clinical study must be monitored and followed up until the end of treatment visits. It is the responsibility of the investigator that any necessary additional therapeutic measures and follow-up procedures are performed.
6.6.7 Overdose

In case of a significant overdose of a study drug, this has to be reported as a serious adverse event.

7 DATA MANAGEMENT UND STATISTICAL ASPECTS

7.1 DATA MANAGEMENT

All data will be recorded in a validated computer database system, incorporating a complete electronic audit trail. Data entry will be performed twice by at least two persons independently. The double entry will be validated and cross-checked by a computer programme.

Patients will be informed that data on their disease and its course will be stored in an pseudonymized way. Each patient has the right to know which information has been stored electronically.

7.2 BIOSTATISTICAL ASPECTS

7.2.1 General design

The present trial is designed as a phase II study which aims at estimating the therapeutic efficacy of the experimental targeted regimen including the HER2 antibody in relation to the known results of the FLOT combination, as to be derived from the AIO FLOT 4 study. The complete pathological response rate (pCR) is chosen as primary efficacy endpoint.

7.2.2 Sample size calculation

Based on the available experience with FLOT, a pCR rate after chemotherapy alone is assumed to be about 10%. This assumption will be validated by the results from the ongoing AIO FLOT 4 trial. The statistical calculation is based on the following premises and assumptions:

- The experimental therapy would be rated as insufficiently active, if the observed pCR rate is 10% or lower, as this corresponds to the expectations after chemotherapy alone.

- On the other hand, the experimental therapy would be considered to be a promising candidate for further development (e.g. in a phase III trial), if the true pCR rate amounted to 20% or more.
• Probability to accept the experimental therapy as promising (> 20% pCR) with respect to efficacy, in spite of a true pCR rate of ≤ 10%: 10% (type I error)

• Probability to reject the experimental therapy as not sufficiently efficient (≤ 10%), although the true pCR rate is promising (> 20%): 20% (type II error, corresponding to a power of 80%).

According to these parameters, and using a standard single-stage phase II design by FLEMING42, \( n = 53 \) patients evaluable for efficacy have to be recruited. Assuming a HER2-positivity rate of 20% about 265 patients have to be screened. The final conclusion of the phase II trial will depend on the definite pCR rate (and its confidence interval) as well as the information on type, frequency and severity of toxicities.

For comparison, design alternatives are shown in the following table:

<table>
<thead>
<tr>
<th>“Futile” pCR rate</th>
<th>Promising pCR rate</th>
<th>Type I error</th>
<th>Power</th>
<th>Patient number</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>20%</td>
<td>5%</td>
<td>80%</td>
<td>69</td>
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<td>10%</td>
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<td>53</td>
</tr>
<tr>
<td>10%</td>
<td>25%</td>
<td>5%</td>
<td>80%</td>
<td>33</td>
</tr>
</tbody>
</table>

7.2.3 Evaluation categories of patients

Patients not fulfilling the selection criteria of the trial (“non-eligible”) will be excluded from the statistical analysis. Only casuistic reports will be provided for this group. All other patients will primarily be evaluated in an intent-to-treat analysis (ITT).

Sensitivity analyses of efficacy endpoints will be performed on the per protocol analysis set defined as the subset of the ITT analysis set who have received all four cycles of pre-operative combination therapy (unless they experience unequivocally documented earlier progression according to RECIST) and who have undergone surgery and who have no major protocol deviations thought to impact on the efficacy conclusions of the trial.

All patients having received at least one application of study therapy are generally evaluable for toxicity.
7.2.4 Statistical methods

All parameters will be evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. If any p values are calculated (e.g. in subgroup/prognostic comparisons), they are considered to be descriptive and will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. Thus the p values will reflect the comparison-wise error and not the experiment-wise error. All p values will be 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 will be checked after data entry. If necessary, the statistical method will be modified accordingly, with critical discussion of the original and modified results.

Response rates (including the primary endpoint), toxicity, and event rates at pre-specified time points are calculated as proportions, providing confidence intervals. In case of comparison between patient groups, these rates will be analyzed by Fisher’s exact test, $\chi^2$ test or Mantel-Haenszel test (or trend test according to COCHRAN/ARMITAGE), respectively.

Event related data like relapse-free or overall survival will be estimated by the product limit method\textsuperscript{43} and eventually compared using the logrank test. If the Peto logrank test\textsuperscript{44,45} is not appropriate because of violation of the proportional hazard assumption\textsuperscript{46}, Gehan’s generalization\textsuperscript{47} of the Wilcoxon rank sum test for censored data (GEHAN 1965) will be applied, preferably in its modification by PETO\textsuperscript{45} (1972) and PRENTICE\textsuperscript{48} (1978). If appropriate, prognostic strata will be taken into account\textsuperscript{45} (PETO, 1977).

Multivariate prognostic analyses will eventually be performed by suitable regression models (logistic regression, proportional hazard regression model\textsuperscript{49}).

7.2.5 Interim and final analyses

A formal interim analysis of safety will be presented to the Independent Data Monitoring Committee (IDMC) after completed documentation of neoadjuvant therapy plus surgery of the first 25 patients (cf. section 11.10).

No formal interim analyses on efficacy are planned. The application of a two-step design, allowing for early stopping in case of insufficient treatment efficacy is not necessary, as all patients receive at least the current standard treatment, which is known to be efficient in this disease.

The main biometrical evaluation of the study and the compilation of the statistical report as part of the integrated clinical/biometrical report will be performed six months after termination of patient recruitment and follow-up as well as after completion and/or correction of all case report forms.
8 STUDY DOCUMENTATION AND ARCHIVING

8.1 DOCUMENTATION AND INFORMATION FLOW

All patient-related data are recorded in a pseudonymized way. Each patient is unequivocally identified by a trial subject number, attributed at recruitment into the study. The investigator has to keep a patient identification log, including the full name and address of the subject and eventually additional relevant personal data such as hospital record number, home physician etc. In addition, patients who were screened in order to be entered into the study, but who could not be recruited for whatever reason (informed consent not given, not fulfilling selection criteria etc.) are recorded in a "patient reject log".

All the data retrieved during the conduct of the study are entered into the appropriate case record forms (CRF) by the investigator or another person authorized by the investigator (co-investigator). The CRFs are provided by the study secretariat and are explained to the investigator by the study monitor.

All recorded data have to be plausible and complete. Please respect the following technical details when using the CRFs:

- Use black or blue ballpoint pens only in order to insure that all copies are legible.
- Write only one letter or numeral into each of the open boxes of the respective data fields. Closed boxes have to be crossed only (check boxes).
- All data fields have to be filled, except for those referring to open questions. If a specific test was not performed or an information item is definitely not available or applicable, information on this should be provided (not done = ND, not applicable, not available = NA, unknown= UK).
- If a date is not known exactly, please fill in the respective field according to the following example: - - 08 05.
- If any corrections have to be performed in the CRF by the investigator or co-investigator, they have to be performed according to GCP principles, i.e. the original entry has to be crossed out but remain legible.
- The correct version is then written legibly beside or above the original one.
- The correction (or addition) has to be dated and signed or initialled.
The investigator is obliged to complete the case report forms within a reasonable time period after retrieval of the data (i.e. usually within 2 weeks). The completed forms are signed by the investigator, where necessary. The original has to be sent to the data management office or handed over to the monitor in case of on-site visits. A copy remains with the investigator. The study office or monitor checks the forms for completeness and plausibility. In case of queries, the form or a photocopy of it will be sent or given back to the investigator for clarification/correction/completion. Queries have to be handled within 4 weeks.

After finalisation of the data checks by the study office/monitor the originals or fair copies are sent to the biostatistical center. If additional queries arise there during computer data entry, they are handled by the investigator via monitor or study office contacts.

8.2 DATA ARCHIVING

The original forms of all relevant study documents including CRFs are stored at the office of the coordinating investigator/sponsor for at least 10 years after completion of the final study report. The investigators have to archive major administrative documents (correspondence with ethical committee, authorities, sponsor etc.), the patient identification log, the signed informed consent forms, and the main study documents (protocol, amendments) for the same time period. The original patient records have to be archived according to the standard procedures of the respective institution, but at least for 10 years.
9 Financing

The sponsor will take care of the financing/funding of the study, according to written agreements between the sponsor and the coordinating investigator, the local principal investigators (or their institutions), the source(s) of funding and other institutions involved in protocol-related procedures.

10 Use of Information and Publication

10.1 Any documents supplied in connection with this study, and not previously published, are considered confidential information. This information includes the clinical protocol, workbooks if applicable, case report forms etc. This confidential information, shall not be disclosed to others without prior written consent from the coordinating investigator and shall not be used except in the performance of this study.

10.2 The information developed during the conduct of this clinical study is also considered confidential. To allow for the use of the information derived from this clinical study and to insure compliance to current regulations, the investigator is obliged to provide the coordinating investigator with complete test results and all data developed in this study.

10.3 The authorship list will be agreed by all investigators prior to publication. The study will only be published once it is completed with respect to the primary endpoint and the corresponding analysis has been performed by the coordinating investigator or his delegate.

10.4 The sponsor recognizes that the investigator has a responsibility to ensure that results of scientific interest arising from the study are appropriately published and disseminated. The Sponsor agrees that the Investigator shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of his own choosing, methods and results of the study, subject to this section 10 and any publication policy described in this section.

10.5 Any publication based on the results obtained at the Investigational Site (or a group of sites) shall not be made before the first multi-centre publication. If a publication concerns the analyses of sub-sets of data from the multi-centred study the publication shall make reference to the relevant multi-centre publication(s).

10.6 Upon completion of the study, and any prior publication of multi-centre data, or when the study data are adequate (in Sponsor's reasonable judgement), the Investigator may prepare the data derived from the study for publication. Such data will be
submitted to the Sponsor for review and comment prior to publication. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee.

10.7 The Investigator agrees that all reasonable comments made by the Sponsor in relation to a proposed publication by the Investigator will be incorporated by the Investigator into the publication.

10.8 The Investigator acknowledges that the Sponsor may present at symposia, national or regional professional meetings, and publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the study and in particular, but without limiting the foregoing, post a summary of study results in on-line clinical trials register(s) before or after publication by any other method. In the event the Sponsor coordinates a multi-centre publication, the participation of the Investigator as a named author shall be determined in accordance with clause 10.3 above and generally accepted standards for authorship. If the Investigator is a named author of the multi-centre publication, such person shall have access to the study data from all Investigational Sites as necessary to participate fully in the development of the multi-centre publication. The Sponsor assures the data of the study to be published in a multi-centre publication within one (1) year after finalization of the Clinical Study Report independent from the study results.

10.9 During the period for review of a proposed publication referred to in clause 6 above, the Sponsor shall be entitled to make a reasoned request to the Investigator that publication be delayed for a period of up to six (6) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its proprietary information and/or Intellectual Property Rights and Know How and the Investigator shall not unreasonably withhold his consent to such a request. The Investigator shall not unreasonably withhold or delay his consent to a request from the Sponsor for an exceptional additional delay if, in the reasonable opinion of the Sponsor, the Sponsor’s proprietary information and/or Intellectual Property Rights and Know How might otherwise be compromised or lost.

11 Ethical and Legal Requirements

11.1 General Requirements and Agreements

The study will be performed according to current legal standards. The ICH E6 Harmonised Tripartite Guideline for Good Clinical Practice, dating from 1997, will be taken into account. In Germany, the requirements according to the following documents will be fulfilled: Deutsches Arzneimittelgesetz (AMG, 15. Novelle, 2009),
"Grundsätze für die ordnungsgemäße Durchführung der klinischen Prüfung von Arzneimitteln" (Bundesanzeiger Nr. 243 vom 30.12.1987) and "Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen" from 3rd November 2006. The coordinating investigator has at least two years of experience in clinical trials on medicinal products. AIO-Studien-gGmbH is the sponsor of the study with respect to GCP regulations (according to article 7 of the EC Commission Directive 2005/28/EC), as the trial at hand is a non-commercial or investigator-initiated clinical trial. The sponsor is responsible for the trial master file according to chapter 4 of the EC Directive 2005/28/EC. The sponsor may delegate this function (or other requirements mentioned in the following sections) to another individual, a company, an institution or an organization.

11.2 DECLARATION OF HELSINKI

The trial will be performed in accordance with the Declaration of Helsinki, as decided upon by the 18th World Medical Assembly, Helsinki, Finland, June 1964 (amended by subsequent World Medical Assembly Somerset West, South Africa, October 1996,). The declaration is included as appendix 5.

11.3 INFORMED CONSENT OF THE PATIENT

Before recruitment into the clinical trial each patient will be informed, that participation in the study is completely voluntary, and that he or she may withdraw the participation in the trial at any time without any declaration of reasons. This will not lead to any disadvantage for the respective patient. If the withdrawal is caused by any adverse drug events, the patient should inform the investigator about this fact.

The treating physician will inform the patient about the drugs to be used and their possible adverse effects. At the same time he/she will be informed on the nature and objectives of the study, expected advantages of the participation, possible hazards of the study and alternatives of treatment. The patient will also receive the necessary information on the trial specific insurance and his obligations with this respect. The patient will have sufficient time for his decision and opportunity to ask additional questions. Moreover, the patient will receive a written “patient information”, containing all relevant information for the patient's decision and the course of the study.

The consent of the patient to participate must be obtained in writing before recruitment into the study. The informed consent form must be dated and signed by
the patient. Thereby, he declares his voluntary consent to participate in the study and his willingness to comply with the requirements of the trial and the instructions of the treating investigator during the course of the study.

There are two copies of the informed consent form: one for the patient and one to be kept by the investigator in his study documents. The informed consent is only valid after receiving the patient's signature. Thereafter, the patient can be entered into the study if he/she fulfils the selection criteria.

With the declaration of consent the patient agrees that data on his disease are recorded within the framework of the clinical trial and that they are transferred to the sponsor in an pseudonymized way. Moreover, the patient agrees that delegates from the responsible authorities or the sponsor may have direct access to his/her original medical records for trial related monitoring, audit, review and regulatory inspection.

11.4 QUALITY ASSURANCE

11.4.1 Standardisation

The evaluation criteria are similar for all participating centers. Each center has to report its normal ranges for haematology and blood chemistry to the coordinating investigator. The respective laboratory institutions have to participate in an appropriate quality assurance program. Toxicity is recorded in a standardized way according to the NCI CTC criteria for categorization and grading. Surgery is performed according to standardized recommendations. Evaluation of response efficacy is performed according to RECIST standards. Pathological efficacy parameters (including the primary endpoint) are determined by central reference pathology.

11.4.2 Monitoring / source data verification

The study will be monitored externally by site visits, written queries and telephone calls to the investigator by authorized personnel of the sponsor representative. Queries or monitoring visits may take place before, during and after recruitment of patients into the study. The number of contacts will depend on the characteristics of the respective center, e.g. the number of recruited patients. According to the investigator's agreement, the monitor is allowed to access the trial documentation and the patients' personal medical records in the participating center.

In order to assure the quality of the data, all entries into the CRFs are formally inspected for completeness and plausibility. During site visits, an additional control with respect to identity of the data recorded in the personal patient records and in the CRF (Source Data Verification) may be performed. The monitor should also review drug accountability records and document retention (study file). Additionally,
the monitor should observe study procedures and will discuss any problems with the investigator.

11.4.3 Audits

In case of an audit by the sponsor or an appropriate authority the investigator will make available all relevant documents. If an audit visit by a regional authority is announced, the respective center should inform the sponsor/coordinating investigator as early as possible in order to allow for an appropriate preparation and support. The inspected investigator or organisational institution of the study will be informed on the result of the audit.

11.5 Registration and Request for Authorisation of the Trial

For approval of the trial the sponsor/coordinating investigator has to issue a request for authorisation according to § 7 Abs. 1,2,4-6 GCP-V to the Paul-Ehrlich-Institut, respectively. At the same time he will issue a request for opinion to his competent ethical committee according to § 7 Abs. 1,2,3,5 and 6 GCP-V. In addition, the request for opinion is sent in parallel to the appropriate “local” ethical committees in Germany, formed according to the law of the respective federal states (§ 7, Abs. 1 GCP-V). On behalf of the individual investigators, the sponsor will also announce all individual trial centers to the respective regional authority, according to § 67 of the Arzneimittelgesetz and § 12 Abs. 1 GCP-V.

The respective federal authority will be informed on the course of the study (in parallel to the competent ethical committee, cf. section 9.5), with respect to safety aspects to be announced (according to § 13 GCP-V, Abs. 1-6) as well as with respect to the termination of the trial and its results (according to § 13 GCP-V, Abs. 8 and 9).

11.6 Ethical Committee

Prior to start of the trial the study protocol and all other requested documents (cf. section 11.5) will be sent to the competent ethical committee by the sponsor and/or coordinating investigator in order to receive its opinion. The trial is only allowed to start when a positive vote of the ethical committee has been received. During the course of the study the sponsor/ coordinating investigator will inform the ethical committee about all study protocol amendments (cf. section 11.7) as well as all SUSARs from the trial according to § 13, Abs. 2 and 3 GCP-V. In addition, the competent ethical committee will receive a report on all SAEs, and/or a statement on the safety of the study subjects once a year or on request during the course of the
study (according to § 13, Abs. 6 GCP-V). If need be, recommendations of the ethical committee will be included in the study protocol.

In addition, the competent ethical committee will be informed by the sponsor and/or coordinating investigator on the course of the study with respect to the termination of the study and its results (according to § 13, Abs. 8 and 9 GCP-V).

Investigators participating in the trial are not allowed to take part in the decision of the ethical committee. A list of the committee members as well as its statutes are included in the trial master file.

11.7 **PROTOCOL AMENDMENTS**

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects (cf. § 10, Abs. 1 GCP-V for the decision criteria) will require a formal amendment to the protocol. Such amendment will be agreed upon by the investigators and the sponsor. It requires a new application to the competent authority and to the competent ethical committee prior to implementation, according to §10, Abs. 2 to 4 GCP-V.

Administrative or technical changes of the protocol such as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, nor on the risk-benefit-ratio, will be agreed upon by the sponsor and the coordinating investigator and will be documented in a memorandum to the protocol. The competent ethical committee may be notified of such changes at the discretion of the sponsor/coordinating investigator.

The sponsor/coordinating investigator has to assure, that all amendments have been added to the study documents at any site involved in the trial. Roche will be informed on any protocol amendment.

11.8 **SUBJECT INSURANCE**

An indemnity insurance will be contracted for the trial subjects in accordance with § 40, Abs. 1, Nr.8 and Abs. 3 AMG. Additionally a accident insurance covering the way to and from the site will be contracted for the trial subjects. The patient will receive all the respective information of relevance to him/her.

In order not to jeopardize insurance protection, any health damage occurring in connection with participation in the clinical trial has to be immediately reported by the subject to the insurance company. The patient has to take all appropriate
measures to identify the cause and extent of the damage as well as to limit its extent, if possible. Especially he/she is obliged to

- report any adverse event or additional medication to the treating investigator
- consult the treating investigator before applying additional medication or other clinical treatment

11.9 INFORMATION ON STUDY DRUGS TO TRIAL INVESTIGATORS

The investigators will receive all relevant and up-to-date clinical and pre-clinical information on the study drugs (SmPC/Fachinformation). When additional data of major relevance for the conduct of the study become evident, they will be distributed to the investigators via an updated version of the existing SmPC or another document containing the information.

11.10 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

A independent Data Monitoring Committee will be established, consisting of three experts in medical oncology, gastrointestinal cancer surgery and/or biostatistics.

The IDMC will receive regular information on safety results of the trial, namely a list of reported SAEs/SUSARs. It will receive and discuss the reports on the interim safety analysis (cf. 7.2.5). Details on the work of the board will be described in a specific IDMC charter, to be jointly agreed upon by the board and the sponsor.

12 REFERENCES


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APPENDICES

1 RECIST Criteria V. 1.1, 2009
2 Siewert Classification of cancers of the gastroesophageal junction, 1987
3 NCI CTCAE V. 4
4 Summary of Product Characteristics (SmPC)
5 Declaration of Helsinki, 1996
6 Central Pathology
7 Rüschoff SOPs
8 Translational Research