Summary of the study protocol of the FLOT3-Study

EudraCT no. 2007-005143-17

Protocol Code: S396

Title

A Prospective Multicenter Study With 5-FU, Leucovorin, Oxaliplatin and Docetaxel (FLOT) in Patients With Locally Advanced, Limited Metastatic or Extensive Metastatic Adenocarcinoma of the Stomach or Esophagogastric Junction- The FLOT3 Study

Endpoints

Summary of chapter 6 of the study protocol

Primary Endpoint

Median Overall Survival (limited versus extensive metastatic disease)

Secondary Endpoints

Pharmacogenetic Risk Profile
Quality of Life
Progression-free Survival (PFS) and Response Rate (Stratum B and C)
R0 Resection rate Stratum A and, if applicable, B
Rate pathological Remissions Stratum A and, if applicable, B
Perioperative Morbidity and Mortality in Arm A and, if applicable, B

Study design / Treatment

Patients with localized, operable (T3/4 and/or N+, M0) or metastatic gastric carcinoma or carcinoma of the esophagogastric junction without prior palliative therapy will be recruited. Prior to enrolment a unique and detailed clinical evaluation of the dissemination of the disease will be done which includes a differentiated regard of the M-category in the TNM classification. A prospective stratification will classify the patients as having either (A) localized and primarily operable, (B) limited metastatic, or (C) extensive metastatic disease. Patients in Stratum A will receive 4 cycles of preoperative FLOT and undergo surgery with curative intention. Then 4 additional postoperative cycles of FLOT will be administered (in total 8 cycles). Patients in Strata B and C also receive 8 cycles of FLOT. Continuation of treatment with for than 8 and to a maximum of 12 cycles is possible in case that a clinical benefit is observed (at the discretion of the investigator), and this only in the absence of dose-limiting toxicities and with consent of the patient in Strata B and C only. Patients in arm B can undergo surgical resection (s. below).
Handling potentially operable patients (summary of chapter 13.1 and 13.2. of the study protocol):

**Stratum A**

Four cycles of FLOT are administered (=8 weeks). Tumor assessment is performed in the second week after the 4th cycle. Then patients proceed to surgery. Patients with disease progression go off study, but still can be operated according to the investigator. For all patients, except those having progressive disease, 4 additional cycles of FLOT are administered in the postoperative period. De-escalation to FLO, OT or FLT is possible at the discretion of the investigator, if the patient does not tolerate an intensive triplet treatment any more. After the end of the 8th cycle, an end of study treatment assessment is performed.

Patients should be offered a comprehensive nutritional consultation directly after the surgery and 2 months later.

**Stratum B**

In patients with limited metastatic disease in whom surgical resection is pursued, investigators will follow the same procedure as for primary operable patients. Patients in stratum B should receive at least 4 preoperative cycles. Surgery should be planned between the 3rd and 4th week after last chemotherapy cycle. Surgery has to be performed with curative or life-prolonging intent (not palliative). Aim of surgery is the complete resection of the primary including lymph node dissection and complete, at least macroscopic, resection or cytoreduction of the metastases (s. chapter 13.4. surgical resection). After operation, within 8 weeks, further 4 postoperative cycles should be administered. De-escalation to FLO, OT or FLT is possible at the discretion of the investigator, if the patient does not tolerate an intensive triplet treatment any more. After the end of the 8th cycle, an end of study treatment assessment is performed. In case of R1-resection or in case of macroscopic tumor rest, patients can be further treated with chemotherapy (s. general discontinuation criteria chapter 14.7.).

**Therapy Schema (Chapter 11 of the study protocol)**

FLOT  
Docetaxel 50mg/m², d1  
5-FU 2600 mg/m², d1  
Leucovorin 200 mg/m², d1  
Oxaliplatin 85 mg/m², d1  
Repeated every 2 weeks (d15)  
8 cycles  

Radiological examinations of reference regions and evaluation of quality of life (by EORTC- QLQ C30, STO22 and LQMN1 forms) are performed before start of study therapy, every 2 months during
and every 3 months after end of therapy until progression or relapse of the disease. Evaluation of quality of life is continued after progression.

Clinical examinations (blood count, assessment of toxicity, anamnensis) are performed every two weeks for evaluation of toxicity and application of chemotherapy. After informed consent is given, 2 ml of peripheral blood of the patient will be analysed for the pharmacogenetic risk profile. Representative tumor material (formalin-fixed and paraffin-embedded) will be analysed within translational projects.

Inclusion Criteria

1. Histologically confirmed, metastatic (any T, any N, M1) or localized operable (uT4, any N, M0 or uT3, any N, M0 or any T, N+, M0) adenocarcinoma of the stomach or gastroesophageal junction[1,2,3,4]
2. no prior cytotoxic chemotherapy
3. Female and male patients ≥ 18 years. Patients in reproductive age must be willing to use adequate contraception during the study and for 3 months after the end of study (Appropriate contraception according to 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 childbearing potential need to have a negative pregnancy test within 7 days before study start.
4. ECOG ≤ 2
5. Leukocytes > 3.000/µl
6. Thrombocytes > 100.000/µl
7. Serum Creatinine ≤ 1.5x ULN, or Creatinine-Clearance > 40 ml/min
8. Written informed consent

1diagnostic laparoscopy is recommended for exclusion of peritoneal metastasis before start of chemotherapy in Strata A and B. In patients with localized, operable carcinoma or with limited metastases, endosonography and esophago-gastro-duodenoscopy for classification of initial stage (u T and N category) should be performed. Pathologically enlarged paraaortal lymphomas are classified as M1 situation (M1 LYMPH). N+ situation is clinically defined as increased number of lymph nodes >1 cm and/or individual lymph nodes >2 cm in radiological and/or endosonographic examination.
2Adenocarcinomas of esophagogastric junction are classified according to Siewert (Siewert 1987).
3In adenocarcinomas of the lower esophagus, affected coeliac lymphnodes are defined as M1 situation.
4Patients with relapse (local or systemic) after curative resection are not eligible for this study. Patients with synchronous metastases (M1) who had surgery due to imminent complications (e.g. bleeding or occlusion) or whose metastasis was previously unknown are eligible for the study under the condition that not all measurable lesions were removed. Resected metastases will be included in classification of affected organs for stratification (Stratum B v C).

Exclusion Criteria

1. Known hypersensitivity against 5-Fluorouracil, Leucovorin, Oxaliplatin or Docetaxel
2. Other known contraindications against 5-Fluorouracil, Leucovorin, Oxaliplatin or Docetaxel
3. Active coronary heart disease, cardiomyopathy or congestive heart failure, NYHA III-IV
4. Malignant secondary disease, dated back < 5 years (exception: In-situ-carcinoma of the cervix uteri, adequately treated skin basal cell carcinoma)
5. Brain metastases
6. Other severe internal disease or acute infection
7. peripheral polyneuropathy > NCI Grad II
8. severe liver dysfunction (AST/ALT>3.5xULN, AP>6xULN, Bilirubin>1.5xULN)
9. Chronic inflammable gastro-intestinal disease
10. inclusion in another clinical trial
11. pregnancy or lactation

Stratification

Stratum A, resectable tumors without distant metastases (cM0).

Stratum B, metastatic tumors with all of the following criteria fulfilled:
- abdominal, retroperitoneal lymph node metastases only (e.g. para-aortal, intra-aorto-
caval, peripancreatic or mesenterial lymph nodes) or a single organ site involved with
  or without retroperitoneal lymph node metastases.
- no clinically (on CT scans or because of ascites) visible or symptomatic
carcinomatosis of peritoneum or pleura and no diffuse peritoneal carcinomatosis on
diagnostic laparoscopy.
- less than 5 liver metastases, if the single organ site is the liver.
- ECOG performance status of 0 or 1.
- serum alkaline phosphatase within normal ranges.
- furthermore, the following specific cases are pre-defined in the protocol: localized
  peritoneal carcinomatosis (P1 or P2) according to the classification of the Japanese
  Research Society for Gastric Cancer [Japanese Gastric Cancer Association 1998] is
  allowed and considered a single organ site. Bi- or unilateral Krukenberg tumors are
  allowed and are considered a single organ site. Uni- or bilateral adrenal gland
  metastases are also considered a single organ site. Extra-abdominal lymph node
  metastases such as supraclavicular lymph node involvement are allowed and are
  considered a single organ site.

Stratum C, metastatic patients who do not fulfill the criteria of Arm B.

Sample Size

250 Patients

Statistics

Sample Size Calculation (Chapter 7 of the protocol)

In this study, the prospective influence of localization and extent of metastases on overall survival of
patients with advanced gastric cancer will be evaluated. Metastatic stage will be assessed by
predefined criteria and patients are allocated to stratum B (limited metastatic) and stratum C (extensive
metastatic). Expected ratio of B:C is calculated as 1:2. In addition, a stratum A is included into the
study consisting of patients with localized, operable tumors. This group is not considered for the
primary hypothesis but is a control group for relatiivation of results in group B and C within identical
study conditions.
Based on previous analyses, the following assumptions for sample size calculation are derived. For stratum C, a median survival of 8 months is expected, and approximately the double time is estimated a reasonable and clinically relevant goal for stratum B (Hazard Ratio 0.55). The hypothesis will be tested one-sided with an alpha error (error of 1st kind) of 2.5%. Assuming a power of 80%, a total of 192 patients in strata B and C have to be included (nB = 64, nC = 128).

Endpoints
Primary endpoint for efficacy of the therapy is overall survival defined as time from on-study date until death. Quality of life will be evaluated by the questionnaires EORTC-QLQ C30, STO22 and LQMNI at baseline and then every two months, if possible also after progression of disease. Progression-free survival (PFS) is defined as time from start of therapy (on-study date) until progression of disease or death of the patient. Safety will be analysed by number, severity and duration of adverse events (with causal relationship to study medication) of all patients who received at least one dose of combination therapy. Adverse events will be reported descriptively by tabulation including CTC grade (CTC-AE version 3). Additionally, serious adverse events will be presented individually with details on severity, duration and outcome of the event (Simon et al. 1997).

In this study, the validation of a pharmacogenetic risk profile for patients with advanced gastric cancer with first-line chemotherapy is planned. Risk parameters were defined in the context of previous clinical studies of our group. Confirmation of a difference of 2.7 months in PFS between a “high-risk” group (HR, PFS 4 months) and a “low-risk” group (HR, PFS 6.7 months) is intended by use of a prospectively defined risk profile. For these analyses, with a hazard ratio of maximal 0.55 and power of 80%, with one-sided significance of 2.5%, a sample size of 100 patients per group is necessary. It can be expected that for a per protocol analysis the planned study population is sufficient for analysis of this endpoint. Allocation to high- or low-risk group will be based on a combined analysis of two genetic polymorphisms of the metabolism of the study substances (XPD312 and MTR2756).

Statistical plan

General parameters:
- First patient in
- Last patient in
- Definition of Population
- Total Population (all patients), no. of patients in the three strata (A, B, C).
- Eligible Population: total population minus patients excluded due to major violation of inclusion criteria; no. of patients in the three strata (A, B, C)
- Safety Population: Patients who received at least one dose of FLOT.
- Listing of patients excluded from the total population, description of reasons

All following parameters should be analysed in the total population and the eligible population
- Baseline Criteria (i.e. demographic data, patient’s characteristics etc.), compared in the three strata (p-values for differences)
- Duration of therapy (days), no. of cycles (median, range), compared in the 3 strata (optional, cumulative doses etc.)
- No. of patients with: 0-4, 5-8, 9-12, >12 cycles in all 3 strata
- Reasons for therapy discontinuation in all 3 strata
- Interruption and dose modification in all 3 strata
- Median Follow-up (+ range) in the total population (months)
- Resection rates curative/non-curative in all 3 strata
- Types of surgery/resection in all 3 strata
- Response rate
- PFS, TTF, OS comparing Stratum A, B and C, with HR, CI 95% Intervals, p-values (Stratum A vs. B; B vs. C); Kaplan-Meier-Curves
- Toxicity (Safety Population) compared between all 3 strata, p-values for differences.
- Perioperative morbidity and mortality defined as adverse events and deaths occurring between surgery date until 30 days later (patients with surgery only); comparison of Stratum A and B.

Subgroup analyses Stratum B:
- Tabulation of baseline characteristics and detailed data relevant for stratification in stratum B for patients with versus without surgery
- PFS, TTF, and OS as described above for patients in Arm B with versus without surgery
- Response rate for patients in Arm B with versus without surgery

Further subgroup analyses:
- Median PFS and OS univariate for following groups within stratum B and C:
  - patients with vs without liver metastases
  - liver metastases >5cm vs rest
  - liver metastases >5cm vs ≤5cm
  - no. of liver metastases >5 vs rest
  - no. of liver metastases >5 vs ≤5 liver metastases
  - liver metastases >5cm or >5 metastases vs rest
  - lung metastasis (presence probable or proven) vs no lung metastasis
  - peritoneal carcinomatosis vs no peritoneal carcinomatosis
  - AP high vs rest
  - ECOG 0 or 1 vs 2
  - One metastatic localization with/without intraabdominal lymphoma vs rest
  - Patients with lymphatic metastases only vs rest
  - Malignant pleural effusion vs rest

- Multivariate analyses of all subgroups described above, Stratum B vs C.

Sensitivity analysis:
- Evaluation of individual significance of all parameters used for stratification in stratum B or C (e.g. PFS and OS analysis stratum B vs C is analysed after exclusion of single parameters)
Study Schema

- Metastatic or localized operable adenocarcinoma of the stomach or gastroesophageal junction
- Age ≥ 18 years
- ECOG ≤ 2
- Adequate hematological and biochemical parameters
- No prior cytostatic chemotherapy in metastatic stage

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<thead>
<tr>
<th>STRATIFICATION</th>
<th>A: resectable</th>
<th>4xFLOT – OP – 4xFLOT</th>
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<tbody>
<tr>
<td>B: limited metastatic</td>
<td>Up to 12xFLOT → secondary OP possible</td>
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<tr>
<td>C: extensive metastatic</td>
<td>Up to 12xFLOT → palliation only</td>
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