NeoFLOT-Trial: Synopsis according to ICH E3 Guideline

1) Name of Sponsor/Company

Klinikum der Universität München-Großhadern
Campus Großhadern
Marchioninistr. 15
81377 München

2) Name of Finished Product

Taxotere ®: Sanofi-Aventis Deutschland GmbH
20 mg/0,5 ml concentrate for solution for infusion
80 mg/2 ml concentrate for solution for infusion

Eloxatin ®: Sanofi-Aventis Deutschland GmbH
5 mg/ml concentrate for solution for infusion

5-Fluorouracil, all in Germany approved pharmaceuticals

Folinic acid: all in Germany approved pharmaceuticals

3) Name of Active Substance

Drug: Docetaxel
Drug: Oxaliplatin
Drug: 5-Fluorouracil
Drug: folinic acid

4) Individual Study Table: Referring to Part of the Dossier (Volume, Page)

Not applicable

5) Title of Study

“NEO-FLOT: A phase II multicentre study of perioperative Chemotherapy for resectable Adenocarcinoma of the Gastroesophageal Junction and of the Stocmach”

„NEO-FLOT: Multizentrische Phase II Studie zur perioperativen Chemotherapie beim resektablen Adenokarzinom des gastrooesophagealen Überganges und des Magens“

Version: 3.0
date: 1st April 2011
EudraCT Nr.: 2008-007546-56
Protocol code: NEO-FLOT

Amendment 1:
In protocol version 2.0 the acquisition of tumor material within a translational research program was planed. No further intervention was scheduled for the patients as existent tumor material from gastroduodenoscopy and surgery was used. The intention of the analysis of the primary tumor was to define prognostic and predictive markers. These markers could be further validated by the analysis of blood samples of the treatment population. In the amendment further details for the acquisition of the blood samples were defined. The benefit-to-risk profile was unchanged by the amendment, as the treatment regimen was not altered and there was no additional hazard for the patients by a single, one-time blood withdrawl.

Amendment 2:
In protocol version 2.1 (July 17th 2010) the study sample size was calculated with an primarily estimated dropout rate of 10%. Accordingly, for 44 patients needed 49 patients should be recruited. After the end of recruitment and a preliminary analysis of the data it became evident that there was an unexpectedly high dropout rate. Additional to an expected dropout rate (due screening failures, withdrawal of informed consent, unacceptable toxicity) unexpectedly often patients were treated with less than the six cycles FLOT without progressive disease. For that reason more patients had to be recruited in the trial. The protocol was amended, increasing the sample size to 59 patients with an estimated drop-out rate of 25% to ensure the statistical power. At first 54 patients were recruited in 12 active study centres. After the acceptance of the amendment of April 2011 5 more patients were recruited to reach the required number of 59 patients for analysis.

6) Investigators

Principal Investigator / „Leiter der klinischen Prüfung (LKP) according to „Arzneimittelgesetz (AMG)“:

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Protocol Comittee:

There was a protocol comittee consisting of 8 specialists from medical oncology, gastroenterology and surgery.

Project management und monitoring:

Project management und monitoring of trial was done by a CRO.

Biostatistics und data management:

Biostatistics und data management of trial was done by a CRO.

Investigators:

There were 10 Principal Investigators (PI) and the LKP active in this trial.

7) Study centre(s)

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8) Publication (reference)

Schulz C, Kullmann F, Kunzmann V, Fuchs M, Geissler M, Vehling-Kaiser U*, et al*. NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma-Very good response predominantly in

patients with intestinal type tumors. International journal of cancer Journal international du cancer. 2015; 137 (3):678-685.

9) Studied period (years):

date of first enrolment: October 13th 2009

date of last enrolment: July 1st 2011

date of last completed: October 9th 2011

There was a temporary recruitment stop due to recalculation concerning the patient numbers needed for analysis. Due to an unexpected high number of drop-outs an amendment was drafted. After the amendment was accepted recruitment was restarted and the trial could be completed.

10) Phase of development

Phase II

11) Objectives

Adenocarcinoma of the gastroesophageal junction (GEJ) and the stomach is a disease associated with poor outcome in most patients. Over the last decades the incidence of distal gastric cancer has declined, whereas proximal gastric cancer and GEJ tumors are on the rise. Only tumors presenting in the stage of limited disease without suspected lymph nodes require sole surgical resection, locally advanced and nodal positive disease should be treated in a multi-disciplinary approach.
Within a perioperative therapy, neoadjuvant chemotherapy aims to reduce the tumor burden, enhances the probability of R0-resection and is also believed to reduce occult micrometastasis Perioperative chemotherapy became a standard of care for resectable adenocarcinoma of the upper GI tract in most Western European countries based on the results of the MAGIC-trial. Including patients with stage II or III resectable adenocarcinoma of the stomach, GEJ and lower esophagus, this study clearly demonstrated the benefit from chemotherapy with three cycles of

the ECF-regimen (epirubicin, cisplatin, 5-fluorouracil) applied before and after surgery as compared to surgery alone. The results of the MAGIC-study were essentially supported by the French ACCORD- trial. In the ACCORD-trial there was a significant higher R0-resection rate and a non-significant decrease in lymph node metastasis in the chemotherapy arm. Data from the MAGIC-trial revealed significantly more less advanced tumors in the pathology report and more resections considered curative by the operating surgeon in the chemotherapy arm. Summarizing, both studies showed that preoperative chemotherapy can induce downstaging and enhanced the possibility of potentially curative R0-resection, thus increasing the probability of disease-free (DFS) and overall survival (OS). At the same time it became evident that adjuvant chemotherapy could only be applied in about half of the patients, which may lead to the hypothesis that the undisputable benefit from perioperative chemotherapy can be induced by the preoperative part of treatment.

The aim of the present trial was, therefore, to investigate an intensified regimen of preoperative therapy. As a chemo- therapy backbone, the biweekly FLO-regimen (5-FU, leucovorin, oxaliplatin) was chosen which was significantly less toxic and at least as effective as the weekly PLF-regimen (cisplatin, leucovorin, 5-FU).

The FLOT-regimen essentially resulted from the addition of docetaxel to the FLO-regimen which was based on the superior efficacy of DCF (docetaxel, cisplatin, 5- FU) compared to standard ECF in the palliative setting. The published evidence indicated a high efficacy and acceptable tolerability of FLOT even in fit elderly patients.

Compared to the MAGIC-study, the present trial sought to intensify preoperative therapy at two levels. (i) The FLOT-regimen includes docetaxel to enhance treatment efficacy. (ii) The prolonged application of FLOT over 12 weeks outnumbers the ECF-therapy of 9 weeks in the MAGIC-trial.

12) Methodology

The study was conducted as a single arm multicenter phase II study and was approved by the local ethics committees of the participating institutions. The trial was listed in ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01160419). All participants gave written informed consent before they entered the trial.

13) Number of patients (planned and analysed)

Assuming an accrual period of 12 to 24 months and a follow-up period of 36 months, testing with a power of 80% at a level $\alpha = 0.05$, a study sample size of 44 patients was needed. With a primarily estimated dropout rate of 10% 49 patients should be recruited. Because of an unexpectedly high dropout rate due to patients being treated with less than the six cycles FLOT, the protocol was amended, increasing the sample size to 59 patients with an estimated drop-out rate of 25% to ensure the statistical power.

14) Diagnosis and main criteria for inclusion

Patients with T3, T4 and/or N1 (according to UICC TNM classification 7th edition, 2009) histologically confirmed gastric adenocarcinoma or GEJ adenocarcinoma (according to the Siewert classification) were eligible. Further inclusion criteria were expected resectability, no prior chemotherapy or radiotherapy, Eastern Cooperative Oncology Group (ECOG) performance status 2, a laparoscopy to exclude peritoneal carcinomatosis visually, age over 18 years, sufficient bone marrow function, serum creatinine 1.25 3 ULN or creatinine clearance 40 ml/min and serum bilirubin 1.25 3 ULN.
Key exclusion criteria were distant metastasis, peripheral neuropathy NCI grade II, cardiac insufficiency NYHA II– IV, uncontrolled medical illness, acute infection or history of other malignancies within the past 5 years.

15) Test product, dose and mode of administration, batch number

Eligible patients received six cycles of neoadjuvant FLOT consisting of 5-FU 2600 mg/m^2 (24-hr infusion), leucovorin 200 mg/m^2 (1-hr infusion), oxaliplatin 85 mg/m^2 (2-hr infusion), docetaxel 50 mg/m^2 (1-hr infusion) repeated every two weeks. The use of granulocyte-colony stimulating factor (G-CSF) was permitted as secondary prophylaxis.

16) Duration of treatment

Patients were treated with six cycles of neoadjuvant FLOT. With a duration of 14 days for one cycle, overall treatment period was 3 months.
Treatment was continued until PD, unacceptable toxicity, patient's refusal, physician's decision or until six cycles were completed. In case of toxicity, study medication was adjusted according to predefined protocol guidelines. Surgical resection including D2-lymphadenectomy was

scheduled within 2–6 weeks after the completion of the last cycle. The surgical procedure was directed by tumor localization and carried out according to hospital-specific guidelines in accordance with the protocol and at discretion of the surgeon. Resection status (R0/R1) and tumor regression were evaluated by a pathologist.

17) Reference therapy, dose and mode of administration, batch number

Not applicable

18) Criteria for evaluation: Efficacy, Safety

Imaging by computed tomography (CT) or magnetic resonance imaging (MRI) of chest and abdomen as well as gastroduodenoscopy and endoscopic ultrasound (EUS) were obtained within 3 weeks before the start of the treatment. After three cycles of FLOT, restaging was performed to identify patients with progressive disease (PD) who were then scheduled to immediate surgery. After six cycles of FLOT, a preoperative restaging was performed with CT or MRI, gastroduodenoscopy and optional EUS. Postoperative imaging was performed every 3 months up to 36 months.

The assessment of response to neoadjuvant treatment was defined by reduction of tumor size, number and size of lymph nodes measured by EUS and CT scan. Response was documented in analogy to RECIST version 1.1 criteria with permission to use further tumor assessment e.g., gastroduodenoscopy to identify patients with PD. Toxicity and adverse events were graded according to NCI-CTC (version 4). Because of a high rate of undetermined histological subtypes, according to the Lauren classification in the reports by local pathologists and deficiently completed case report forms, a central histological review was performed.

19) Statistical methods

In this analysis, date of data cutoff was January 14, 2014.

Prognostic and predictive factors for PFS and OS were estimated by Cox-Regression analysis. The treatment was considered active if the R0-resection rate exceeded 75%. Conversely, the treatment was considered inactive if the R0-resection rate was <60%.

Data monitoring and data collection were performed by an external Clinical Research Organisation. Event-related parameters were analyzed using Kaplan–Meier-estimation,

differences were tested using logrank test and Cox-regression analysis. All data analysis was performed by Statistical Analysis Software SAS (version 9.2).

R0-resection rate was evaluated as the primary endpoint; secondary endpoints included the pathologic complete response (pCR) rate (defined as T0N0), the histologic regression grade according to Becker et al., chemotherapy safety and toxicity, operative and postoperative complications, PFS and OS.

The intent-to-treat (ITT)-population included all registered patients being treated with at least one cycle of chemotherapy. The per-protocol (PP)-population was defined as completing preoperative chemotherapy and undergoing surgery. The primary endpoint was R0-resection rate as assessed in the PP-population. All secondary endpoints were assessed in the ITT-population.

20) Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

Patients, protocol compliance, efficacy results:

From October 2009 to July 2011, 59 patients were recruited from 11 centers in Germany. One patient was excluded due to screening failure.

All patients underwent laparoscopy to exclude peritoneal carcinomatosis. Eight patients were not able to receive surgical resection: neoadjuvant chemotherapy was terminated due to patient's refusal in one patient, due to bleeding from the tumor in one patient and due to death in two patients. In two patients, functional inoperability was observed during surgery, while two patients received chemotherapy after PD.

In two patients surgery was performed after 3 cycles due to PD. Surgery was performed in one patient after five cycles. Another patient received one cycle of FLOT and five cycles of FLO due to an allergic reaction to docetaxel.

The primary endpoint, R0-resection rate was 86.0% (43/50 patients, per-protocol analysis (PPA)). Comparing to the initial clinical tumor classification with the posttherapeutic pathological assessment, downstaging within the PP-population was observed with regard to T-stage in 59.6% and N-stage in 51.1% of the patients.

In the PPA, 10 patients (20%) achieved a complete pathological remission (pCR) (Becker score Grade 1a) (1 of the 10 patients with pCR with signet cell histology) and 10 tumors (20%) showed <10% intact tumor cells (Becker Score 1b). Among these very good responders, 85% had intestinal type tumors, 10% (2/ 20) had diffuse and 5% (1/20) had mixed type tumors. The

pCR rate in the ITT-population was 17.2% (10/58). The median number of lymph nodes analyzed was 23 (range 10–50).

Median follow-up time was 24.5 months. Median DFS was 32.9 months (event rate 25/50 patients). With an event rate of 48.3% (28/58) the median OS was not reached. In the ITT-population the 1-year survival-rate was 79.3%, the 1-year PFS-rate was 67.2%. A subgroup analysis of all patients undergoing surgery revealed a significantly longer OS for patients with Becker score 1a/1b compared to Becker score 2/3 while patients with intestinal type tumor showed a significantly longer OS and an improved PFS compared to non-intestinal type tumor.

Toxicity, safety results:

Median dose intensity over all cycles was 89.2% (docetaxel 90.4%, oxaliplatin 89.9%, leucovorin 93.3%, 5-FU 90.7%). Dose reductions were carried out in 25 patients (43.1%). Major reasons for dose reduction or protocol discontinuation were toxicity (38 pts, 65.5%) and patient's wish (3 pts, 5.2%).

The most common hematological toxicities NCI-CTC Grade 3–4 included neutropenia (17 pts, 29.3%) and leukopenia (14 pts, 24.1%). Febrile neutropenia occurred in one patient (1.7%). The most common gastrointestinal Grade 3–4 toxicities were diarrhea, in seven (12.1%), mucositis in four (6.9%) and nausea in three patients (5.2%). Grade 3 and 4 neurosensory toxicity was diagnosed in three patients (5.2%). Treatment-related mortality was observed in two patients due to sepsis (3.4%) that was not associated with febrile neutropenia. One patient was 79-years old and had a medical history of coronary heart disease. The other patient (73-years old) suffered from cardiac hypertrophy, hypertension and diabetes. Another two patients died due to postoperative complications.

Application of adjuvant chemotherapy was explicitly not part of the protocol and was administered in 39/58 patients (67.2%). Main reasons for not initiating adjuvant therapy were: reduced medical condition (13.8%), patient's wish (6.9%) and death (6.9%). Additional two patients received adjuvant chemoradiotherapy, one patient of the ITT-population turning out to be functionally inoperable was treated with palliative chemoradiotherapy.

Conclusions:

The NeoFLOT-trial is among the first to investigate prolonged docetaxel-based neoadjuvant chemotherapy.

The R0-resection rate of 86% in NeoFLOT-study relates to the R0-resection rate of representative trials obtained after preoperative therapy. pCR in the NeoFLOT-trial was 20%

(10/50 pts) which compares favorably to recently published taxane-based trials reporting pCR rates in the range of 10–14% (PP analysis). Among the patients archeiving pCR, 8/10 of the tumors were intestinal-type and 2/10 were diffuse-type (1 with signet cell histology). In patients with total or subtotal histopathological regression (Becker score 1a and 1b) intestinal type was pre- dominant with 85% (17/20).

Adjuvant therapy was explicitly not part of the NeoFLOT trial and was given at the discretion of the local investigator. After surgery, 72.4% of patients (42/58; ITT-population) received adjuvant therapy, the majority (38.5%) continuing with the FLOT-regimen. This high percentage of adjuvant chemotherapy exceeds the results from some studies, but is comparable to recent reports where adjuvant chemotherapy was started in 72.5% and 67% of patients.

The safety profile of neoadjuvant FLOT is in accordance with data derived from the palliative setting. Undoubtedly, the addition of a taxane adds to toxicity and increases the risk of hematological and non-hematological side-effects. In the present trial, leukopenia (24.1%) and diarrhea (12.1%) were identified as predominant, but acceptable Grade 3–4 toxicities. Feasibility of neoadjuvant FLOT, in general, may be indicated by a median dose intensity of 89.2%. The observation of two treatment-related deaths, however, clearly directs the attention to careful patient selection.

In conclusion, this study indicates that intensified neoadjuvant chemotherapy with 6 cycles of FLOT is feasible, highly effective and tolerable in resectable gastric adenocarcinoma and gastroesophageal junction adenocarcinoma. Very good response (pCR and <10% residual tumor) was predominantly observed in patients with intestinal type tumors. The optimal duration of the treatment as well as the relevance of tumor response with regard to proper selection of adjuvant therapy remains important issues to be clarified by future studies.

21) Date of report

February 2nd 2017