Protocol Synopsis

Title:
Neoadjuvant Chemoradiotherapy and Adjuvant Chemotherapy with 5-Fluorouracil and Oxaliplatin versus 5-Fluorouracil Alone in Rectal Cancer

This study is ongoing but not recruiting participants.

Study Start Date: July 2006
Primary Completion Date: October 2011
Estimated Study Completion Date: December 2014

Sponsor:	University of Erlangen-Nürnberg Medical School
Information provided by:	University of Erlangen-Nürnberg Medical School
ClinicalTrials.gov Identifier:	NCT00349076
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1. Selection of Patients, including both Eligibility and Ineligibility Criteria

Patients matching all inclusion criteria and none of the exclusion criteria listed below will be recruited in 88 participating centers.

Inclusion Criteria:

- Males and females aged ≥ 18 years, inclusive, at screening
- Histologically proven, advanced primary carcinoma of the rectum (tumor > 12cm above the anal verge), with clinically staged T3/4 or any node-positive disease
- No prior cancer-specific therapy except a diverting stoma
- ECOG PS ≤ 2
- Adequate bone marrow function: Leukocytes > 3,5 x 10^9/L, absolute Neutrophil count > 1,5 x 10^9/L, Platelet count > 100 x 10^9/L, Hemoglobin > 10 g/dL
- Adequate hepatic function: Total bilirubin < 2,0 mg/dL ALAT, ASAT, alkaline phosphatase, gamma-GT < 3 x ULN 7. Serum creatinine < 1,5 mg/dL, creatinine clearance > 50 mL/min
- Written informed consent by the competent patient

Exclusion Criteria:

- Pregnant or breast feeding women
- Fertile patients without adequate contraception during therapy
- Past or ongoing drug abuse or alcoholic excess
- Prior application of chemotherapy
- Prior application of radiotherapy to the pelvis
- Prior (within 4 weeks) or concurrent treatment with any other investigational agent
- Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- History of severe somatic or psychological diseases: - instable cardiac disease not well controlled with medication, myocardial infarction within the last 6 months:* Central nervous system disorders or psychiatric disability including dementia or epileptic disease; * active uncontrolled intercurrent infections or sepsis
- Peripheral neuropathy > 2 (NCI CTC AE grading)
- Previous or concurrent malignancies, with the exception of adequately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix. The inclusion of patients with other adequately treated tumors within the last 5 years has to be discussed with the principal investigator
- Chronic diarrhea (> NCI CTC AE-Grade 1)
- Known allergy to substances containing platinum compounds
- Concurrent use of the antiviral agent sorivudine or chemically related analogues
- Known dehydropyrimidindehydrogenase (DPD) deficiency

2. Schema and Treatment Plan, including Administration Schedule

2.1 Overview

This is a multi-center, open-label, parallel-group, randomized, phase III treatment trial in patients with histologically proven advanced primary adenocarcinoma of the rectum (tumor < 12cm from the anal verge) with clinically staged T3/4 or any node-positive disease

Approximately 1200 patients in 88 participating centers in Germany will be randomly assigned to receive either

Experimental Arm A (800 patients): Preoperative simultaneous chemoradiotherapy (5-Fluorouracil and Oxaliplatin), TME-surgery, and adjuvant chemotherapy (oxaliplatin, calciumfolinat, 5-Fluorouracil)

or

Active Comparator Arm B (800 patients): Preoperative simultaneous chemoradiotherapy (5-Fluorouracil), TME-surgery, and adjuvant chemotherapy (5-Fluoruracil).

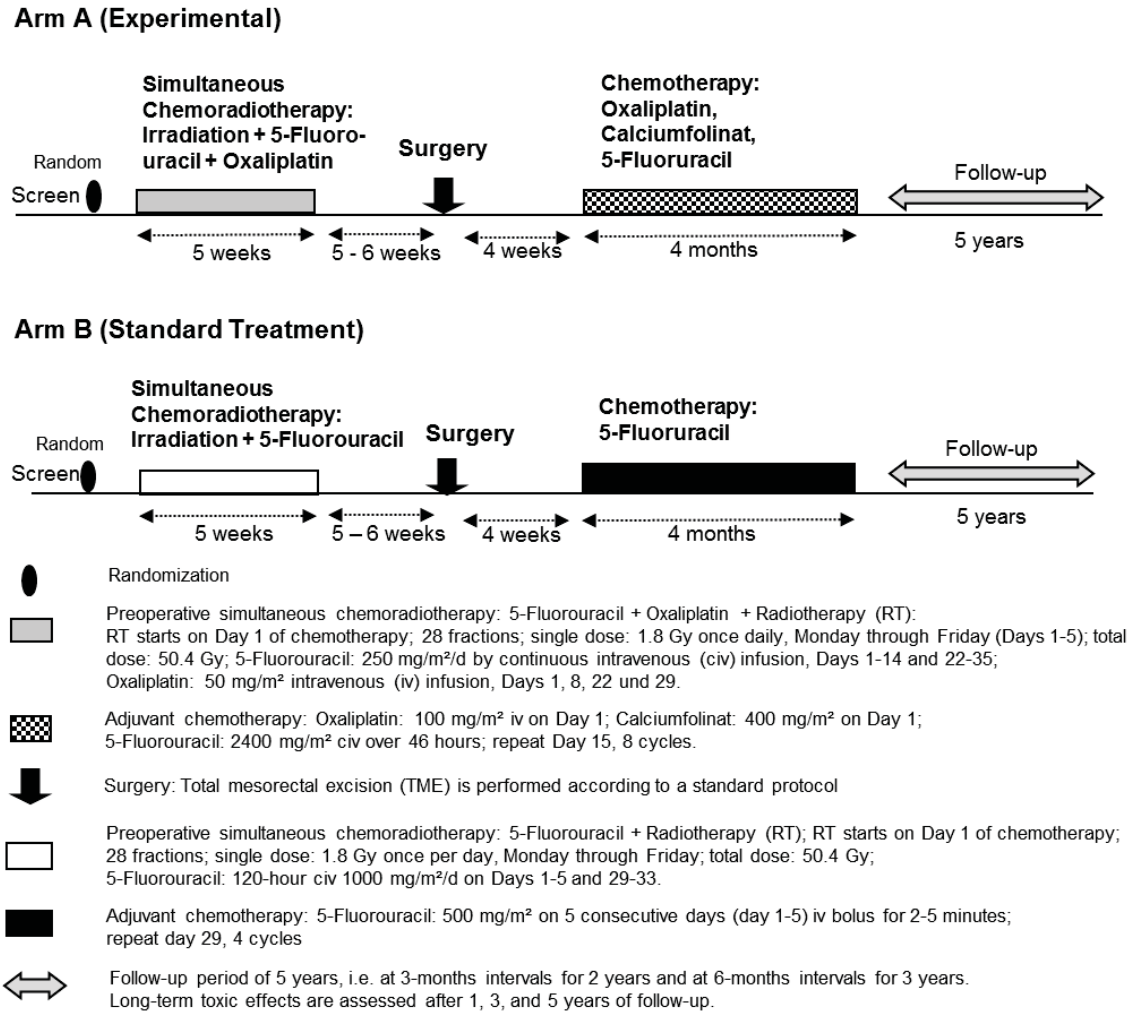

Figure 1: Study schedule of events for Study CAO/AIO/ARO-04.

2.2 Schedule of Events

2.2.1 Pre-Treatment

Informed Consent
Informed Consent is obtained prior to any study-specific screening procedures.

Screening:
Assessment of eligibility to ensure all inclusion- and none of the exclusion criteria are met.

Randomization:
Random treatment assignment is performed centrally and is stratified by study center, clinical T-category (cT1-3/cT4), and clinical N-category (cN0/cN1-2).

2.2.2 Treatment

Arm A (Experimental):

Preoperative Radiotherapy
Radiotherapy consists of 28 daily fractions; single dose: 1.8 Gy per day, Monday through Friday, for 5 weeks. Total dose: 50.4 Gy, delivered with a minimum of 6 MV photons through a three- or four-field box technique to the primary tumor, mesorectal, presacral and internal iliac lymph nodes up to the level of the promontorium.

Preoperative Concurrent Chemotherapy
Concurrent chemotherapy with Oxaliplatin, Calciumfoliat and Fluoruracil: 5-Fluorouracil: 250 mg/m²/d by continuous intravenous (civ) infusion, Days 1-14 and 22-35; Oxaliplatin: 50 mg/m² intravenous (iv) infusion, Days 1, 8, 22 und 29.

Recovery
There is a recovery period of 5-6 weeks after chemoradiotherapy.

Surgery
Total mesorectal excision is performed according to a standardized technique.

Recovery
There is a recovery period of 4 weeks after surgery.

Adjuvant Chemotherapy
Oxaliplatin: 100 mg/m² iv on day 1; calciumfolinat: 400 mg/m² on Day 1; 5-Fluorouracil: continuous intravenous (civ) infusion of 2400 mg/m² over 46 hours; repeat Day 15, 8 cycles.

Arm B (Active Comparator):

Preoperative Simultaneous Radiotherapy
Radiotherapy consists of 28 fractions; single dose: 1.8 Gy once per day, Monday through Friday, for 5 weeks. Total dose: 50.4 Gy. Radiotherapy is delivered with a minimum of 6 MV photons through a three- or four-field box technique to the primary tumor, mesorectal, presacral and internal iliac lymph nodes up to the level of the promontorium.

Preoperative Concurrent Chemotherapy:
Concurrent chemotherapy with Fluorouracil: Administration during Week 1 and 5 of preoperative radiotherapy: civ infusion over 120 h with 1000 mg/m² (on Days 1-5 and 29-33), 4 cycles

Recovery
There is a recovery period of 5-6 weeks after chemoradiotherapy.

Surgery
Total mesorectal excision is performed according to a standardized technique.

Recovery
There is a recovery period of 4 weeks after surgery.

Adjuvant Chemotherapy
5-Fluorouracil: 500 mg/m² on 5 consecutive days (day 1-5) iv bolus for 2-5 minutes; repeat on Day 29, 4 cycles.

2.2.3 Assessment of Safety

During therapy, patients are monitored weekly for signs of acute toxic effects, with appropriate adjustments in chemotherapy and radiotherapy made as necessary. Assessment of perioperative and 30-day postoperative complications included anastomotic leakage, perineal complications, bleeding, ileus, fistulas, and death.

2.2.4 Follow-up

Over a follow-up period of 5 years, long-term toxic effects are assessed at 1, 3, and 5 years post treatment. Evaluations consist of physical examination, a complete blood count, and blood chemical analysis. Proctoscopy, abdominal ultrasonography, CT of the abdomen, and chest radiography are also used, according to guidelines of the German Cancer Society.[1] Histopathological confirmation of local recurrence (defined as a tumor within the pelvis or the perineal scar) and of distant recurrence is encouraged; acceptable alternative approaches included sequential radiologic studies to detect the enlargement of a mass. The physicians evaluating patients' relapse status are aware of the treatment assignments.

3. Rules for Dose Modification

3.1 Toxicity and Adverse Events

Acute toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events, v 3.0 (CTC AE). In case of adverse events which do not result in severe or life-threatening consequences as judged by examining physician (e.g. alopecia), treatment should not be modified. If several different kinds of toxicity occur, the most vigorous dose reduction step should be applied.

If an adverse event can be traced back exclusively on one cytostatic agent or specifically on the radiotherapy (e.g., hand-foot syndrome by continuous 5-FU infusion, neurotoxicity by oxaliplatin) the dose of the other drug or of radiotherapy does not have to be modified. If dose reduction becomes necessary, the reduced dosage will be kept until end of pre-operative chemoradiotherapy or of adjuvant chemotherapy, respectively. A new escalation is not allowed. If toxicity requires therapy interruption of more than two weeks, the patient will be removed from the study for toxicity reasons.

3.2 Control arm with 5-FU: Guidelines for dose modifications

During per-operative chemoradiotherapy and between the adjuvant chemotherapy cycles, bone marrow depression, diarrhea, stomatitis and occasionally hand-foot syndrome is expected. Continuation of the chemotherapy might be postponed by one week, however, regarding the pre-operative setting, should be within the radiotherapy frame.

For simultaneous chemoradiotherapy, the following guidelines for chemoradiotherapy have been defined:

- Leucocytes > 3.500 cells/µL and platelets > 100.000 cells/µL: normal dosage
- Leucocytes > 2.500 cells/µL and platelets > 80.000 cells/µL: pause for one week at maximum, if above referenced limits are not reached: switch to 75% of normal dose
- Leucocytes < 2.500 cells/µL and platelets < 80.000 cells/µL: Postponement until limits are reached

A dose reduction in the next 5-FU cycle to 75% is also envisaged if the patient exhibits the following side effects:

- Diarrhea > grade 1
- Mucositis > grade 1
- Hand-foot syndrome > grade 1

In case of grade III mucositis, grade III diarrhea, or grade III hand-foot syndrome the 5-FU chemotherapy will be discontinued until only side effects have improved to grade I. Thereafter, 5-FU therapy will be continued with 75% dosage. An exception is diarrhea, which is frequently observed during radiotherapy. In this case, postponement and dose reduction of 5-FU to 75%, as individually judged be the examining physician, should only be performed if grade III diarrhea continues for more than 72 hours despite of proper antidiarrhoic medication. A prerequisite for this procedure is a regular control of the patient, which is usually guaranteed by daily visits at the radiotherapy departments. In case of grade IV toxicity, chemotherapy will be stopped immediately. In this case, restoration of the chemotherapy is only possible after consultation with the study center.

3.3 Experimental arm with 5-FU and oxaliplatin: Guidelines for dose modification during pre-operative chemoradiotherapy

The combination of irradiation with 5-FU and oxaliplatin constitutes, with regard to toxicity and recommended dose adjustments, a specific situation in comparison to the established recommendations for dose adjustments for adjuvant or palliative chemotherapy:

1. There are overlapping toxicities of all three agents (in particular, diarrhea, eventually bone marrow toxicity).

2. The typical toxicities of the 5-FU continuous infusion (hand-foot syndrome) and of oxaliplatin (neuropathy) should not occur or at least at minor intensity within the pre-operative setting since the cumulative doses are low.

3. It is always intended not to interrupt radiotherapy and to perform it completely. In general, the dose modifications of the adjuvant setting (see Section 3.4) are also valid for the pre-operative setting.

3.4 Experimental arm with 5-FU (+folinic acid) and oxaliplatin: Guidelines for dose modification during adjuvant chemotherapy

If 5-FU or oxaliplatin toxicity at start of an adjuvant chemotherapy cycle necessitates postponement of a treatment cycle, both drugs should be postponed. Treatment should be restored only if both drugs are applicable again. If oxaliplatin has finally to be stopped, treatment should be continued if 5-FU can be given again. If oxaliplatin could not be administered due to toxicity reasons, 5-FU (+folinic acid) is administered at identical dosage (no augmentation!). If 5-FU has finally to be discontinued, the entire chemotherapy will be stopped (i.e., monotherapy with oxaliplatin is not intended).

For dose modifications of 5-FU/folinic acid it is critical whether toxicities occur

1. in the interval between to courses

2. at the day of planned iv application of oxaliplatin and 5-FU or

3. during infusion of 5-FU

If toxicity occurs in the interval between two chemotherapy courses, upon restoration, dose reduction of 5-FU/folinic acid is performed according to the following table.

Table 1: Dose Modification for 5-FU/folinic Acid in Case of Toxicity between two Chemotherapy Courses

	CTC Grade			
	1	**2**	**3**	**4**
Leucocytes	100%	100%	5-FU: 75%	5-FU: 75%, folinic acid: 75%
Platelets	100%	100%	5-FU: 75%	5-FU: 75%, folinic acid: 75%
Mucositis	100%	100%	5-FU: 75%	5-FU: 75%, folinic acid: 75%
Diarrhea	100%	100%	5-FU: 75%	5-FU: 75%, folinic acid: 75%
Skin	100%	100%	5-FU: 75%	Stop

If

- Diarrhea > grade 1
- Mucositis > grade 1
- Leukopenia > grade 2
- Thrombocytopenia > grade 1
- Other toxicities > grade 2

are observed at next day of 5-FU/oxaliplatin application, therapy has to be discontinued for one week until normalization of the gastrointestinal toxicity and leucocytes are > 3.000/µl and platelets > 100.000/µl. If these limits are not reached within one week, waiting for another week is recommended.

The neurotoxic events caused by oxaliplatin are handled as follows:

Table 2: Dose Modification following Neurotoxic Events caused by Oxaliplatin

	Duration of Toxicity		
	1 to 7 days	**> 7 days**	**Between Cycles**
Chilliness dysaesthesia	no change	no change	no change
Paraesthesia	no change	no change	-25%
Paraesthesia with concomitant pain	no change	-25%	5-FU: continue folinic acid: stop
Paraesthesia with functional impairments	no change	-50%	5-FU: continue folinic acid: stop

For a small proportion of patients (1-2%), a specific kind of acute neuropathy is observed, termed laryngopharyngeal dysaesthesia syndrome, which is characterized by subjective feeling of dysphagia and dyspnea without any evidence for objective airway constriction. This syndrome is not life-threatening and rapidly reversible without treatment. In the following cycles, infusion of oxaliplatin should be extended to 6 instead of 2 hours.

The toxicity of oxaliplatin is judged according to the following scale:

Table 3: Scale for the Assessment of Oxaliplatin Toxicity

Toxicity Grade	**Definition**
Grade 1	paraesthesia/ dysaesthesia < 7 days
Grade 2	paraesthesia/ dysaesthesia 8 to 14 days
Grade 3	paraesthesia/ dysaesthesia > 14 days
Grade 4	paraesthesia/ dysaesthesia with functional impairments

If hypersensitivity reactions toward oxaliplatin occur, resumption of chemotherapy with oxaliplatin should be considered individually upon careful risk estimations and only if the allergic symptoms were rather mild (consultation with the principal investigator and with the oncological reference center is advised).

4. Measurement of Treatment Effect including Response Criteria, Definitions of Response and Survival, and Methods of Measurement

4.1 Primary Endpoint

The primary endpoint is disease-free survival (DFS) at 3 years defined as the interval from randomization to locoregional or metastatic recurrence or the appearance or a secondary colorectal cancer or death, whichever occurs first.

4.2 Secondary Endpoints

- Resection rate
- rate of sphincter preservation
- tumor regression
- cumulative incidence of local and distant recurrences
- overall survival
- toxicity
- quality of life

5. Reasons for early Cessation of Trial Therapy

If toxicity requires therapy interruption of > 2 weeks, the patient will be removed from the study for toxicity reasons.

Throughout the study, patients may be subject to medical assessment and review of compliance before continuing in the study. Patients must continue to meet the inclusion and exclusion criteria during the study, including restrictions related to contraception, if applicable, and medication use. Noncompliant patients may be discontinued from the study.

Every patient will be informed that participation in the study is voluntary and that consent can be withdrawn at any time without the need to provide reasons, and without disadvantage or prejudice.

6. Objectives and Entire Statistical Section (Including Endpoints)

6.1. Statistical Endpoints and Hypothesis

Primary endpoint:
To show superiority of the addition of oxaliplatin to neoadjuvant chemoradiotherapy (N-CRT) and to 5-FU-based adjuvant chemotherapy (experimental arm) in comparison to standard N-CRT followed by adjuvant 5-FU monotherapy (control arm) in terms of DFS within three years of follow-up (primary endpoint).

DFS is defined as the time frame between day of randomization and the first day of occurrence of at least one of the following items:
• R2 resection
• local relapse following R0 or R1 resection
• evidence of distant metastasis
• death of the patient

If none of the aforementioned events occur for a randomized patient within the follow-up time, the patient will be censored at the first day at which at least one of the following events occur:
• end or truncation of the study
• study dropout by patient's initiative

The null hypothesis of this study is that there is no statistically significant difference between the experimental and the control arm.

Secondary endpoints were classified as:
• R0 resection rate, circumferential resection margins, quality of TME-surgery
• TNM-classification, number of investigated lymph nodes after quality controlled TME-surgery
• proportion of sphincter-preserving surgical procedures
• tumor regression grading
• cumulative incidence of local relapses and distant metastasis
• overall survival after five years
• acute toxicity of radio- and chemotherapy according to CTC criteria
• late toxicity of radio- and chemotherapy

6.2 Sample Size Calculation for the Entire CAO/ARO/AIO-04 Study

In the experimental arm (i.e. the neoadjuvant chemoradiotherapy with 5-FU) within the precursor study CAO/ARO/AIO-94, DFS after three years was 74.9% (Fig. 1). This treatment now serves as control arm and as the basis for sample size calculation of the CAO/ARO/AIO-04 study. When assuming a 82% DFS for the intensified chemoradiotherapy with oxaliplatin and protocol violations of 5% in both treatment arms, about 1200 patients (600 in each arm) will be necessary to achieve a power of 80% at 5% significance level with the log-rank test (Fig. 2 and Figure 3). Sample size estimation was performed as described in Lachin & Foulkes (1986) [2].

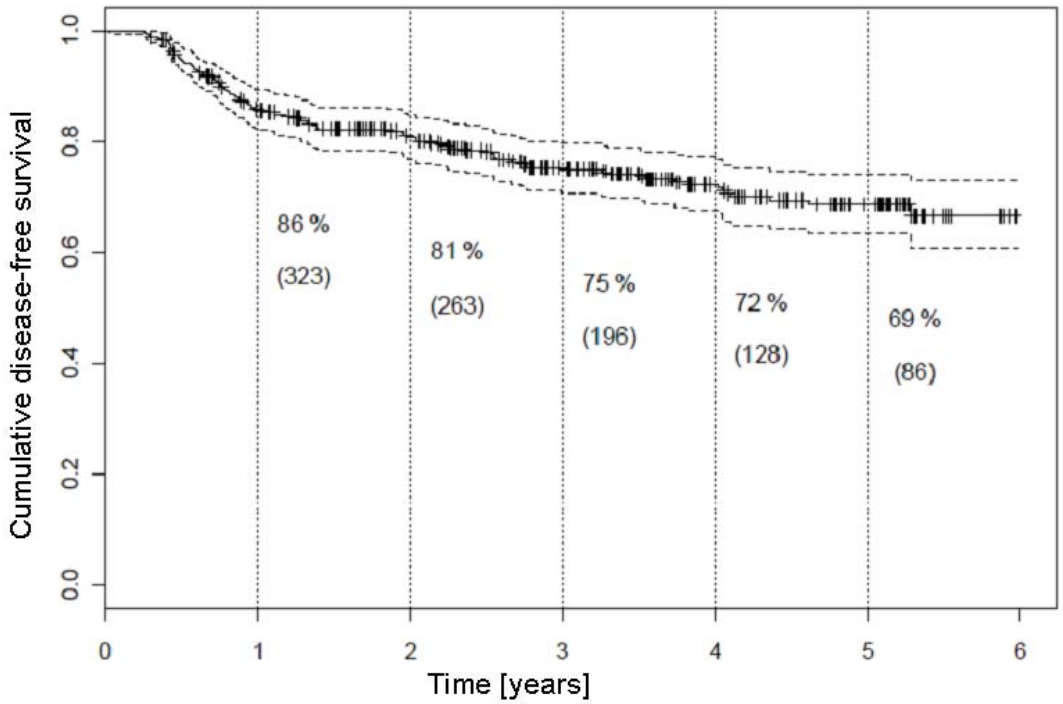

Fig. 1 **Disease-free survival for 406 patients in the neoadjuvant arm (i.e. chemoradiotherapy with 5-FU) of the precursor CAO/ARO/AIO-94 study (Sauer 2004 [3]). Percentages and absolute numbers of patients at risk for the considered time points are indicated.**

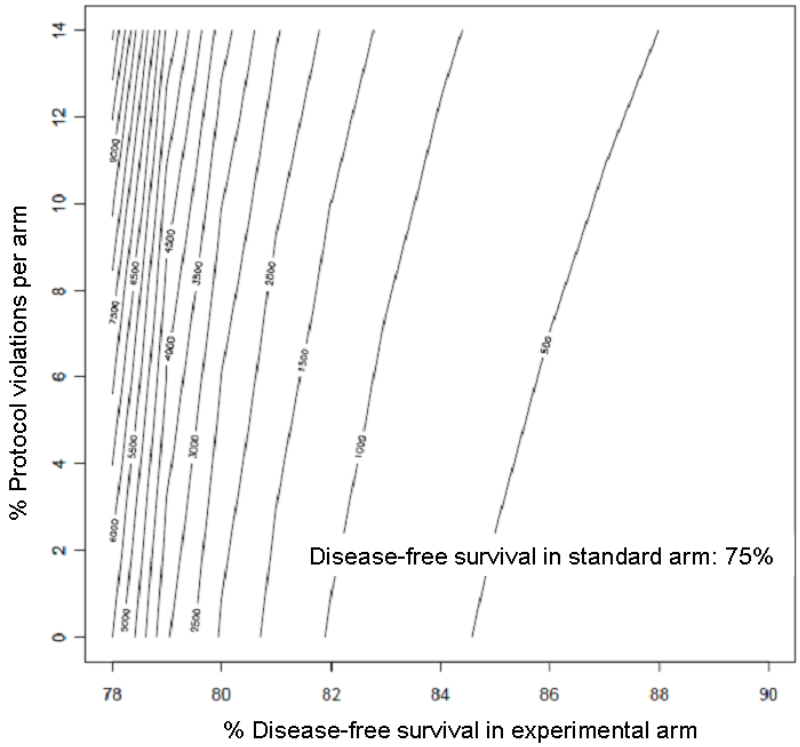

Fig. 2 **Sample size required to achieve 80% power for the log-rank test with a recruitment period of 3 years and minimal follow-up of 2 years in dependence on disease-free survival in the experimental arm and the rate of protocol violations.**

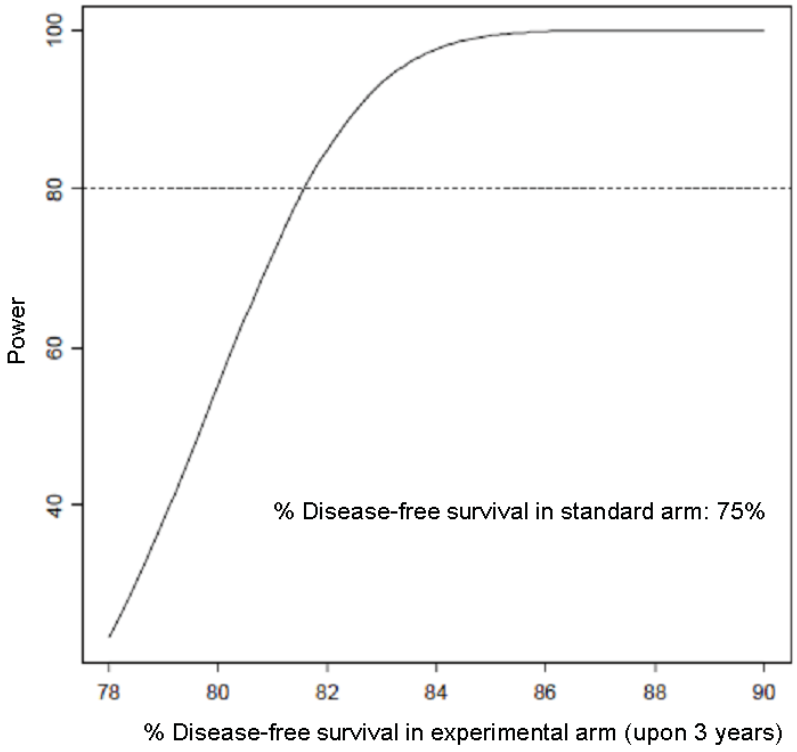

Figure 3 **Power of log-rank test at a significance level of 5% in dependence on disease-free survival for n=1200 patients.**

6.3 Analysis cohorts

The 'intent-to-treat' population refers to all randomized patients with the study arm defined by randomization, regardless of protocol violations, stop of treatment, or time of follow-up.

The 'per-protocol' population is composed of all patients who started therapy. The patients will be analyzed in the therapy arm where they were actually treated, regardless of randomization. For the interim safety analyses all randomized patients will be considered who started therapy.

6.4 Statistical Analysis

6.4.1 Testing the Primary Endpoint

The hypothesis concerning the primary endpoint, as defined in Section 6.1, is based on the 'intent-to-treat' population assessed by log-rank statistics. The reference distribution under the null hypothesis of equal DFS in both arms will be derived from the asymptomatic conditional distribution of the log-rank statistics for each participating center and in relation to the most prognostic factor, the lymph node status at time of randomization. That corresponds to stratification according to participating centers and dichotomous lymph node status. The effect size is defined by the point estimator with 95% confidence interval of the hazard ratio. If the null hypothesis can be rejected at level of 5%, the experimental treatment will be established. The primary endpoint will be visualized by Kaplan-Meier survival curves.

6.4.2 Interim Analyses

Since planning of the required sample size harbors uncertainties both for methodological reasons such as assumptions of distributions as well as for the estimation of the effect size, a sequential procedure enabling adaption of the study protocol in terms of sample size makes sense. An interim analysis, which is conducted upon minimal follow-up time for half of the patients, could be carried out at the soonest at 3.5 years after start of study, i.e. when the recruitment phase is completed and the last patients have been treated. Therefore, interim analyses have to be restricted on the confirmatory analysis of secondary endpoints referring to treatment safety. These analyses will be performed annually, starting one year after start of study and will result in study stop if a relevant increase in toxicity in the experimental arm is observed (see Section 6.4.4).

In order to postulate superiority of the experimental arm as early as possible and to be able to offer this treatment to newly diagnosed patients, an interim analysis can be conducted if at least 50% of the recruited patients have completed the minimal follow-up time of two years. In this case, the nominal level of 5% will be divided according to Kim and DeMets 1987 [4]. Thereby, data are based on the proportion of patients with completed follow-up time (DeMets 1985 [5], DeMets 1989 [6]).

6.4.3 Explorative Analyses

All analyses of secondary endpoints including interim safety analyses are of explorative nature, in particular, no adjustment for multiple testing will be performed. Censored secondary endpoints will be analyzed analogously to the method described in Section 6.4.1. Nominal endpoints will be tested for equivalence in both study arms by means of chi-square statistics derived from contingency tables, ordinal variables by linear statistics. All tests will be performed via stratification for participating center and lymph node status. For visualization, Kaplan-Meier survival curves (in case of censored secondary endpoints) or mosaic plots (in case of contingency tables) will be used.

6.4.4 Safety Analyses

The safety analyses are based on toxicity grades I to V. In general, due to the known neurotoxicity of oxaliplatin a trend to higher toxicity grades is assumed, however, the following limits must not be exceeded:

• not more than 5 percent absolute increase in grade V toxicity in the experimental compared to the control arm

not more than 5 percent absolute increase in grade V toxicity in the experimental compared to the control arm

• not more than 20 percent absolute increase in grade IV toxicity in the experimental compared to the control arm

• not more than 30 percent absolute increase in grade III toxicity in the experimental compared to the control arm

The initial safety analysis will be conducted six months after study begin, if at least 50 patients in each arm have completed therapy, otherwise at that time point at which at least 50 patients in each arm have completed therapy. Thereafter, safety analyses will be carried out annually an refer to the patient cohort as described in Section 6.3.

6.4.5 Prognostic Factors

If the null hypothesis could be rejected, all known clinical impact variables will be investigated for their power to predict the primary endpoint. Therefore, different regression models will be evaluated like Cox model, fractional polynomials (Sauerbrei 1999 [1]), survival trees (LeBlanc 2002 [7], Schumacher 2001 [8]) in a manner as they have been established for the colon carcinoma by Radespiel-Tröger et al. [9], as well as ensembles of survival trees (Hothorn 2004 [10]). The suitability of the different models will be evaluated in terms of prognosis quality (Graf 1999 [11]).

7. References

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