Multi-institutional Phase I/II Study:

Neoadjuvant chemoradiation with 5-FU and oxaliplatin combined with deep regional hyperthermia in locally recurrent rectal cancer (HyRec Trial)

- Study Protocol -

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EudraCT Nr.: **Version:** Draft 0.2 from 07.03.08 / AH

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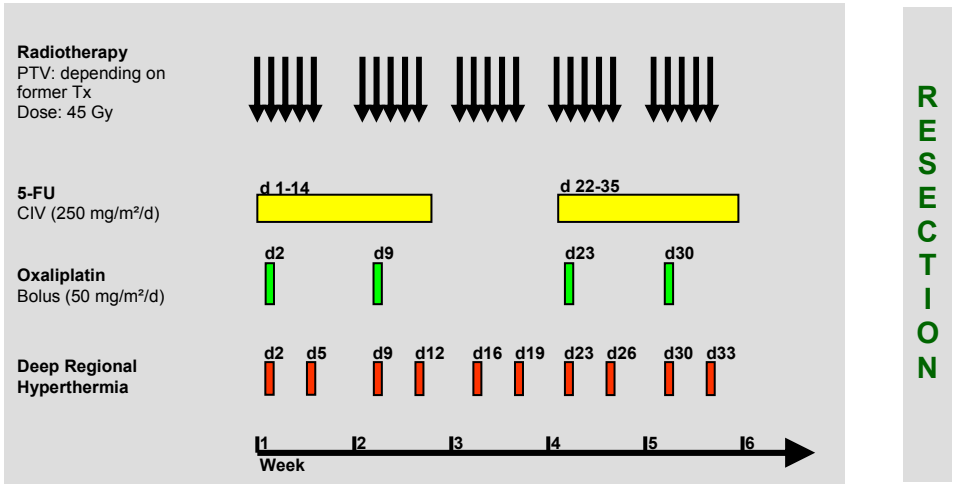
STUDY SYNOPSIS

Protocol title	Neoadjuvant chemoradiation with 5-FU and oxaliplatin combined with deep regional hyperthermia in locally recurrent rectal cancer (HyRec-Trial)
Study design / phase	Multi-institutional phase II study
Objective of the study	To decide upon the feasibility of a multimodal regimen consisting of radiochemotherapy and hyperthermia
Primary endpoints	• Feasibility rate (i.e. rate of patients not experiencing dose-limiting toxicity [DLT]) • Number of hyperthermia applications by patient
Secondary endpoints	• Local progression-free survival • Distant metastasis-free survival • Overall survival • Response rate (RECIST criteria) • Rate of curative resections (R0) • Rate of acute and late toxicity according to NCI CTC, and postoperative morbidity

Flow chart



Inclusion Criteria

- Age ≥ 18 years
- Life expectancy ≥ 2 years
- Histologically confirmed locally recurrent (resectable or non-resectable) adenocarcinoma of the rectum
- ECOG-performance status < 2
- Sufficient bone marrow function:

  WBC > 3,5 x 10^9/l
  Neutrophil granulocytes > 1,5 x 10^9/l
  Platelets > 100 x 10^9/l
  Hemoglobin > 10 g/dl
- Sufficient liver function:

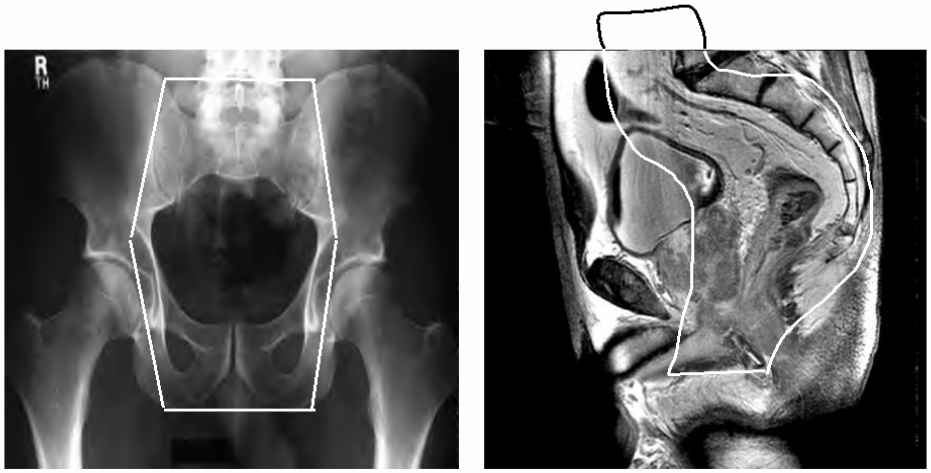
  Bilirubin < 2,0 mg%

  SGOT, SGPT, alkaline phosphatase, gGT less than 3 times upper limit of normal
- Serum creatinine < 1,5 mg%, glomerular filtration rate > 50 ml/min
- Signed study-specific consent form prior to therapy
- Fertile patients must use effective contraception during and for 6 months after study treatment
- Considered fit for oxaliplatin and 5-FU containing combination chemotherapy.

Exclusion criteria

- Pelvic radiotherapy during the last 12 months
- Pregnant or lactating/nursing women
- Distant metastasis (M1)
- Drug addiction
- On-treatment participation on other trials
- Active intractable or uncontrollable infection
- Prior or concurrent malignancy (≤ 5 years prior to enrolment in study) except rectal cancer or non-melanoma skin cancer or cervical carcinoma FIGO stage 0-1 if the patient is continuously disease-free
- Chronic diarrhea (> NCI CTC-Grad 1)
- Chronic inflammatory disease of the intestine
- Collagen vascular disease
- The presence of congenital diseases with increased radiation sensitivity, for example ataxia teleangiectatica, or similar
- Pre-existing uncontrolled cardiac disease, signs of

	cardiac failure, or rhythm disturbances requiring therapy • Myocardial infarction within the past 12 months • Congestive heart failure • Complete bundle branch block • New York Heart Association (NYHA) class III or IV heart disease • Known allergic reactions on study medication • Cardiac pacemaker • Disease that would preclude chemoradiation or deep regional hyperthermia • Any metal implants (with exception of non-clustered marker clips) • Psychological, familial, sociological, or geographical condition that would preclude study compliance • Patients deemed technically unsatisfactory for deep regional hyperthermia
Planned number of patients	n = 59 (evaluable for feasibility)
Planned number of institutions	to be determined
Planned duration of recruitment and follow-up	Recruitment: 2 years Follow-up of each patient: up to 5 years
Treatment	***Radiotherapy (no prior pelvic irradiation)*** Patients undergo radiotherapy once daily, 5 days a week, for 5 weeks. Patients receive 45 Gy (25 x 1.8 Gy) to the pelvis (ICRU-report 50). The pelvic radiotherapy uses a three or four field box technique and at least 6 MV photon beams. The field borders for pelvic irradiation are confined as follows:



Patients with tumors that are considered as not resectable after 45 Gy receive a 3D-conformal boost to the gross tumor volume with a security margin of 1-2 cm in every direction to a total dose of 59.8 Gy, at least. Patients with tumors that are considered as resectable receive surgery in curative intention 4-6 weeks after completion of chemoradiation.

Radiotherapy (prior pelvic irradiation)

Patients undergo 3D-conformal radiotherapy once daily, 5 days a week, for 5 weeks. Patients receive 45 Gy (25 x 1.8 Gy) to the gross tumor volume with a security margin of 1-2 cm in each direction (ICRU-report 50). Radiotherapy uses 6 MV photon beams, at least.
Patients with tumors that are considered as not resectable after 45 Gy receive a 3D-conformal boost to the gross tumor volume with a security margin of 1-2 cm in every direction. The total dose is left to the discretion of the local radiotherapist. Patients with tumors that are considered as resectable receive surgery in curative intention 4-6 weeks after completion of chemoradiation.

Chemotherapy

Patients receive simultaneous chemoradiation with 5-FU and oxaliplatin:
5-FU: 250 mg/m²/d as continuous intravenous infusion; d1-14 and d22-35
Oxaliplatin: 50 mg/m2 i.v., on the days 2, 9, 23, 30. Given as two hours bolus infusion in 500 ml Glucose 5%.

Deep regional hyperthermia (RHT)

Hyperthermia is scheduled twice weekly during the time of external radiotherapy and started within one hour before or after irradiation to a total of 10 treatments. The interval between two RHT-treatments has to be a minimum of 72 hours. Thermometry probes have to be positioned in the rectum (if accessible), the bladder, the vagina and the rima ani for continuous thermometry and thermal mapping of tumor-related temperatures. Therapeutic time starts when the tumor-related temperature in the rectum reached a minimum of 41.5°C or 30 min after enabling power. Therapeutic time is scheduled to be 60 min, the maximum total duration should not exceed 90 min.

Surgery

Curative resection will be tried 4-6 weeks after chemoradiation if no contraindications are present. Contraindications may be infiltration of the sacral vertebras 1 and 2 or infiltration of the basal pelvic muscles.

1 SCIENTIFIC BACKGROUND AND RATIONALE

1.1 RECTAL CANCER

1.1.1 General aspects

Colorectal cancer is the second most frequent cancer cause of death in most of the developed countries, with about 50.000 new cases per year in Germany. Almost half of the colorectal primaries are located in the rectum[1]. The most important curative treatment modality is radical surgery (R0), which is recommended as a single modality in early stages (pT1/pT2 pN0). In stage II (pT3/pT4 pN0) and stage III patients (pN+) the rate of local and/or distant recurrences after surgery alone increase distinctly, thus requiring additional (neo)adjuvant therapy. Pre-operative concurrent radiochemotherapy and post-surgical adjuvant chemotherapy is currently considered as standard of care in many countries, e.g. Germany.

1.1.2 Local recurrence in rectal cancer

1.1.2.1 Incidence

The incidence of local recurrence in patients with an initial diagnosis of locally advanced, stage II/III rectal cancer has decreased dramatically (to 5 – 20%) during the last decade since the introduction of total mesorectal excision and (neo)adjuvant radiochemotherapy[2,3]. In the first German Rectal Cancer Study (CAO/ARO/AIO-94), establishing the state-of-the-art of treatment in Germany, the local recurrence rate after 5 years was as low as 6% in the group with neoadjuvant treatment, compared to 13% in the adjuvant group[4]. Nevertheless, assuming a slightly higher local failure rate outside of clinical trials, at least 2000 cases will still be diagnosed in Germany every year, with most of them having received a full radiotherapy course during primary treatment[5].

While, in general, the prognosis is still poor, the therapeutic situation of the patient with local relapse may be a curative or a palliative one. Once isolated local recurrence is diagnosed, only a minority of patients present with resectable disease[6]. Due to the mostly intensive pre-treatment, local re-therapy has become considerably more difficult, from the points of view of technical feasibility and patient's tolerance. Most patients are in an incurable situation, often suffering from severe pain and other symptoms. Therefore, effective palliation of symptoms and preservation of a good quality of life are the major goals for most of these patients.

1.1.2.2 Surgery

Curative-intent surgery represents the most important factor to achieve local control and long-term survival in rectal cancer patients with isolated pelvic recurrence[3,5]. Resectability rates of up to 30% have been reported in retrospective series, with long term survivors amounting to a maximum of 35%[7,8,9]. This has been confirmed by the findings of a large randomised trial on adjuvant radiotherapy, where 7% of patients with stage II/III primary disease presented with isolated local recurrence during follow-up. Of these, 37% were resectable with free margins, resulting in a 5-year survival rate of 20%[10].

Even if curative resection is not an option, surgery plays a role in the palliative armamentarium for the treatment of recurrent disease[3].

1.1.2.3 Radiotherapy

In case of unresectable local recurrences, radiotherapy remains the main option for re-treatment, as it is usually well tolerated, reliably induces symptom relief and may improve local tumour control[11,12,13] or even achieve cure in rare cases[3]. However, doses considered necessary for tumour eradication can often be delivered only to patients who were not irradiated primarily. As a result, symptom control is only provided for a limited period of time[2.6,14].

1.1.2.4 Chemotherapy

Systemic chemotherapy alone is generally believed to be not effective enough to warrant local control in patients with locally recurrent rectal cancer, even if novel agents like oxaliplatin or irinotecan are applied[5]. However, a possibly relevant palliative effect may be achieved, even in the absence of an objective tumour remission[15].

1.1.2.5 Combined modality treatment

Obviously, none of the different modalities currently available in locally recurrent rectal cancer is effective enough by itself to provide long-term tumour control in a majority of patients[5]. As has been shown in primary treatment, the synergy of different treatment techniques might offer better results. However, most published data on multimodal concepts refer to only small, heterogeneous or selected patient populations. Radiochemotherapy including 5-FU showed promising results in a group of 59 pre-irradiated patients, with 35% R0 resection rate and a 5 year survival rate of 39%[16]. The assumption, that the introduction of novel cytostatics or biological agents may further improve the results, has not yet been shown in larger trials[17].

However, the observation that neoadjuvant radiochemotherapy of not pre-irradiated local recurrences was found to enable curative resection in up to 80% of the patients[17,18], indicate that multimodal treatment concepts appear to be the most promising way to improve therapy results in recurrent rectal cancer in the near future[7,14].

1.2 HYPERTHERMIA

1.2.1 General aspects

Hyperthermia, defined as an elevation of tissue temperature in the range of 40-43° Celsius has been under active investigation as a cancer treatment modality, both singly and more often in combination with radiotherapy and/or chemotherapy, for much of the last half of the twentieth century[19]. Numerous *in vitro* studies, both cellular and in animal systems, have demonstrated synergistic effects between radiotherapy and hyperthermia with a thermal enhancement ratio (TER) of up to 2.5[20,21]. Numerous phase II clinical trials have shown an approximate doubling of the complete response rate of solid tumours to the combination of heat and radiotherapy compared with radiotherapy alone. Several phase III trials have been carried out as well, confirming the efficacy suggested by the phase II trials, in diseases such as breast carcinoma[22,23], melanoma[24,23], and head and neck cancer[25,26].

Two randomized clinical trials already proved beneficial effects for the combination of hyperthermia with radiotherapy and radiochemotherapy in the treatment of primary rectal cancer: Berdov et al.[27] reported on 115 patients with T4NXM0 rectal cancer that received radiotherapy alone in the control group (n=59) and radiotherapy combined with hyperthermia in the experimental group (n=56). Complete and partial remission rates (16 vs. 2% and 54 vs. 34%; $P<0.05$) as well as overall survival rates at five years (36 vs. 7%; $P<0.05$) were significantly improved in the experimental group. Rau et al.[28] reported on a randomized trial with 137 patients with uT3 and uT4 rectal cancer that were treated with neoadjuvant radiochemotherapy combined with (n=69) or without (n=68) simultaneous deep regional hyperthermia. Response (complete and partial remission rates) was significantly better for the hyperthermia group (66 vs. 49%; $P<0.05$). Time to progression at three years was better, as well (66 vs. 49%; $P<0.05$).

1.2.2 Hyperthermia in recurrent rectal cancer

Only few reports exist on combined modality treatment regimes including hyperthermia for recurrent rectal cancer. Endpoints of the following studies were feasibility and palliation.

Juffermans et al.[29] evaluated the palliative effect of reirradiation and hyperthermia in patients with unresectable, recurrent colorectal carcinoma in 54 patients. The total reirradiation dose varied from 24 Gy to 32 Gy given in fractions of 4 Gy twice weekly. Three or four hyperthermia treatments were given once weekly. The described combined treatment was feasible and well tolerated. Comparison of results from radiotherapy plus hyperthermia with results after radiotherapy alone suggested that additional hyperthermia prolonged the duration of palliation.

Schaffer et al.[30] analysed treatment and follow-up data of 14 patients with local recurrence of rectal cancer who were treated with radiation therapy (RT), chemotherapy (CT), and regional hyperthermia (RHT). Nine of these patients had received irradiation and CT (= pre-treated patients) in the past. For this group, 30.6-39.6 Gy RT, 5-fluorouracil (5-FU) as a continuous infusion over 5 days per week (350 mg/m²/24 h) combined with RHT twice a week was given. The 5 remaining patients (= not pre-treated) received conformal irradiation of 45 Gy with a boost between 9 and 14.4 Gy, combined with continuous infusion of 5-FU on days 1-4, and 29-33 (500 mg/m²/ 24 h), and RHT twice a week. Among 13 evaluated cases, the overall objective response rate was 54% (5 complete responses, 2 partial responses). At mean follow-up of 13.9 months (range 5-32 months) 7 patients were alive. The therapeutic regimen appeared to be active in the treatment of local recurrences of rectal cancer.

Hildebrandt et al.[15] reported on a pilot study of nine preirradiated patients with local recurrence of rectal cancer treated with chemotherapy and hyperthermia. Hyperthermic chemotherapy was applied according to a modified 'OFF'-schedule with weekly infusions of 43 mg/m² of oxaliplatin (i.v., 120 min), 500 mg/m² of folinic acid (i.v., 120 min) and 2.6 g/m² of continuous infusional 5-fluorouracil (24 h) for 6 consecutive weeks. Oxaliplatin was started in parallel to pelvic radiofrequency hyperthermia that was provided by the BSD 2000-system. A total of 67 applications were administered to nine patients and were well tolerated. A total of 55/67 (82%) chemotherapy courses were applied without dose-reduction. In 62/67 (93%) hyperthermia sessions, a treatment time of > 60 min was maintained. Eight out of 10 episodes of severe (WHO III degrees) toxicity represented typical side-effects of the chemotherapy given (nausea n = 4, diarrhoea n = 3, neuropathy n = 1). Two severe adverse events were firstly attributable to hyperthermia (haematuria, n = 1; deterioration of a decubital ulcer, n = 1). No patient suffered disease progression according to WHO criteria during the treatment period. Two patients achieved a partial remission. It is concluded that hyperthermic chemotherapy with oxaliplatin, folinic acid and 5-FU is feasible. Overall toxicity was moderate. Results, moreover, suggest a relevant palliative effect in patients with pre-irradiated pelvic recurrence of rectal cancer.

1.3 RATIONALE OF THE STUDY

For patients with locally recurrent rectal cancer there is no standardized treatment regimen, especially for the subgroup with a prior pelvic radiotherapy in the history. The curative potential of surgery, radio-, and chemotherapy as sole treatment option is very limited. Therefore, a combined modality treatment approach is mandatory. Surgery as well as radiochemotherapy are established in the treatment of recurrent rectal cancer. But treatment results are still not satisfying[31]. Hyperthermia has proved to be feasible in combination with radio- and chemotherapy[15,29,30]. Two randomized trials for locally advanced rectal cancer showed that additional hyperthermia is able to increase the response rate and to prolong the time to progression[27,28].

Wiig et al.[31] studied the clinical outcome in patients with complete pathologic response (pT0) to preoperative irradiation/chemo-irradiation operated for locally advanced or locally recurrent rectal cancer. Four hundred and nineteen patients had preoperative irradiation (46-50 Gy/2 Gy fractions) for primary locally advanced (PLA) or locally recurrent (LR) rectal cancer. 141 PLA and 65 LR cases with R0 resections/M0 stage were studied. Two of the pT0 PLA patients had also been given sensitizing chemotherapy and two pT0 in the LR group had received pelvic hyperthermia as well. pT0 was achieved in 7% of 229 PLA and 8% of 190 LR patients. For the PLA group, actuarial 5-year survival of pT0 was 90% versus 53% for the pT > 0 group. The difference was statistically significant. At five years local recurrence was zero in pT0 patients versus 23% in pT > 0. For the LR groups 5-year-survival was 62% for pT0 versus 45% for the other pT-stages, local recurrence was 17 and 35% respectively.

In summary, there is some evidence that radiochemotherapy combined with deep regional hyperthermia can improve response, local control and survival rates in patients with recurrent rectal cancer. The present trial aims at showing, that potent new chemotherapeutic agents such as oxaliplatin can be incorporated in a multimodal treatment regimen including hyperthermia with a high degree of feasibility.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

Primary objective of the study is to decide upon the feasibility of the combined modality regimen consisting of chemoradiation including 5-FU/oxaliplatin and deep regional hyperthermia by assessment of the rate of patients without dose-limiting toxicity (DLT). In addition, the number of applied hyperthermia treatments by patient will be determined.

2.2 SECONDARY OBJECTIVES

Secondary endpoints are:

- Local progression-free survival
- Distant metastasis-free survival
- Overall survival
- Response rate (RECIST criteria)
- Rate of curative resections (R0)
- Rate of acute and late toxicity according to NCI CTC, and postoperative morbidity

3 STUDY DESIGN

3.1 TYPE OF STUDY

Exploratory multi-institutional phase I/II feasibility and efficacy study.

3.2 PATIENT NUMBER

59 patients evaluable for the primary feasibility endpoint are required.

3.3 TIME SCHEDULE

Start of recruitment:	July 2008
Planned termination of recruitment:	June 2010
Planned termination of follow-up:	June 2015
Final study report:	September 2015

4 PATIENT SELECTION

4.1 INCLUSION CRITERIA

- Age ≥ 18 years
- Life expectancy of ≥ 2 years
- Histologically confirmed, locally recurrent (resectable or non-resectable) adenocarcinoma of the rectum (any recurrence of tumor within the lesser pelvis)
- ECOG-performance status < 2
- Sufficient bone marrow function:

  WBC > 3,5 x 10^9/l
  Neutrophil granulocytes > 1,5 x 10^9/l
  Platelets > 100 x 10^9/l
  Hemoglobin > 10 g/dl
- Sufficient liver function:

  Bilirubin < 2,0 mg%

  SGOT, SGPT, alkaline phosphatase, gGT less than 3 times upper limit of normal
- Serum creatinine < 1,5 mg%, glomerular filtration rate > 50 ml/min
- Signed study-specific consent form prior to therapy
- Fertile patients must use effective contraception during and for 6 months after study treatment
- Considered fit for oxaliplatin and 5-FU containing combination chemotherapy.

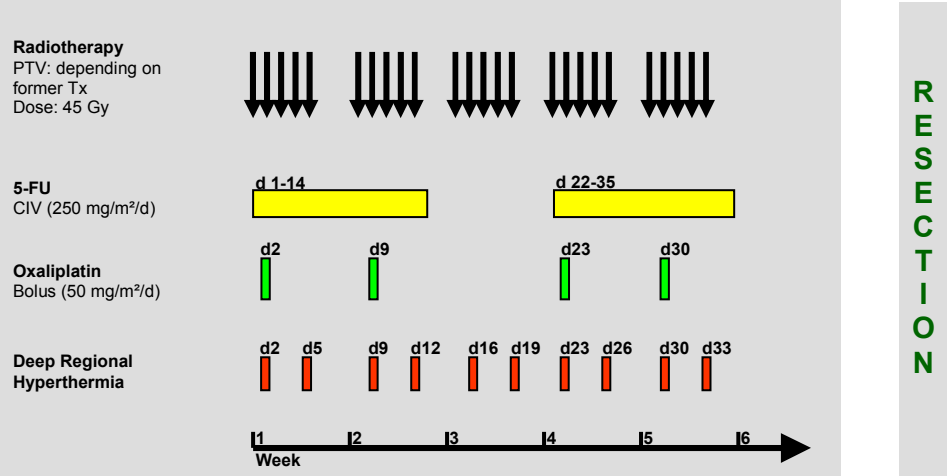
No study treatment or any other procedure within the framework of the trial (except for screening) will be performed in any patient prior to receipt of written informed consent.

4.2 EXCLUSION CRITERIA

- Pelvic radiotherapy during the last 12 months
- Pregnant or lactating/nursing women
- Distant metastasis (M1)
- Drug addiction
- On-treatment participation on other trials
- Active intractable or uncontrollable infection
- Prior or concurrent malignancy (≤ 5 years prior to enrolment in study) except rectal cancer or non-melanoma skin cancer or cervical carcinoma FIGO stage 0-1 if the patient is continuously disease-free
- Chronic diarrhea (> NCI CTC-Grad 1)
- Chronic inflammatory disease of the intestine
- Collagen vascular disease
- The presence of congenital diseases with increased radiation sensitivity, for example ataxia teleangiectatica, or similar
- Pre-existing uncontrolled cardiac disease, signs of cardiac failure, or rhythm disturbances requiring therapy
- Myocardial infarction within the past 12 months
- Congestive heart failure
- Complete bundle branch block
- New York Heart Association (NYHA) class III or IV heart disease
- Known allergic reactions on study medication
- Cardiac pacemaker
- Disease that would preclude chemoradiation or deep regional hyperthermia
- Any metal implants (with exception of non-clustered marker clips)
- Psychological, familial, sociological, or geographical condition that would preclude study compliance
- Patients deemed technically unsatisfactory for deep regional hyperthermia

5 TREATMENT

5.1 OVERVIEW



Radiotherapy (no prior pelvic irradiation):

45 Gy to the pelvis, once daily, 5 days a week for 5 weeks (25 x 1.8 Gy). If not resectable after 45 Gy, 3D-conformal boost to a total dose of 59.8 Gy.

Radiotherapy (prior pelvic irradiation):

45 Gy to the gross tumor volume with a security margin of 1 – 2 cm in each direction, once daily, 5 days a week for 5 weeks (25 x 1.8 Gy). If not resectable after 45 Gy, 3D-conformal boost to a total dose which is left to the discretion of the local radiotherapist.

Chemotherapy:

5-FU	250 mg/m²/d as continuous infusion, day 1-14 and day 22-35
Oxaliplatin	50 mg/m² i.v., d2, 9, 23, 30

Deep regional hyperthermia (RHT):

Twice weekly (minimum interval: 72 h) during the time of external radiotherapy and started within one hour before or after irradiation to a total of 10 treatments.

Surgery:

Curative resection (not part of the experimental study treatment) will be tried 4 – 6 weeks after chemoradiation.

5.2 STUDY MEDICATION

5.2.1 Distribution and accountability of study medication

5-FU and oxaliplatin are generally available for the routine treatment of advanced colorectal cancer, and thus, will be prescribed by the treating physician, as this prescription is within the framework of standard, approved usage.

5.2.2 General information of 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 6) for both drugs.

5.2.3 5-Fluorouracil

5-FU has been a widely used standard drug in the treatment of colorectal cancer for almost five decades. It is generally available under numerous brand names. An example SmPC (“Fachinformation”) is included in Appendix 6, providing all required information on the drug.

5-FU is administered on the basis of milligrams of drug per square meter of body surface area (BSA) as measured at baseline, up to a maximum of 2 m², in a dose of 250 mg/m²/d as continuous infusion, day 1-14 and day 22-35.

Dose-limiting adverse effects of 5-FU include stomatitis, diarrhea and myelosuppression. Cardiotoxicity (chest pain similar to angina pectoris, arrhythmias, or even sudden cardiac death) are very rare events.

5.2.4 Oxaliplatin

5.2.4.1 Calculation of oxaliplatin dose

Doses for oxaliplatin will be administered on the basis of milligrams of drug per square meter of body surface area (BSA) as measured at baseline (mg/m^2), up to a maximum value of 2 m², and should be rounded to the nearest 10 mg.

5.2.4.2 Administration of oxaliplatin

Oxaliplatin will be administered as a 2-hour intravenous infusion. In case of pharyngolaryngeal dysaesthesia oxaliplatin should be administered as 6-hour infusions.

Oxaliplatin diluted in 500 mL of 5% glucose solution must be infused either via a peripheral vein or central venous line over 2 hours. The infusion line must be adequately flushed with 5% dextrose solution (D5W) between oxaliplatin infusion and the administration of any other drug.

Oxaliplatin is incompatible in solution with alkaline medications or media and must not be mixed with these or administered simultaneously through the same infusion line. Do not simultaneously administer other drugs by the same infusion line.

Needles or intravenous administration sets containing aluminium parts that may come in contact with oxaliplatin should not be used. Aluminium has been reported to cause degradation of platinum compounds.

Oxaliplatin administration does not require hyperhydration. In the event of extravasation, administration must be discontinued immediately.

5.2.4.3 Possible adverse effects of oxaliplatin

Anaphylactic/anaphylactoid reactions

As is the case for other platinum compounds, hypersensitivity and anaphylactic/anaphylactoid reactions have been reported. These allergic reactions were similar in nature and severity to those reported with other platinum-containing compounds, i.e. rash, urticaria, erythema, pruritis, and, rarely, bronchospasm and hypotension. These reactions occur within minutes of administration (can also occur at other than the first cycle of treatment) and should be managed with appropriate supportive therapy (e.g. standard epinephrine, corticosteroid, and antihistamine therapy). Drug-related deaths associated with platinum compounds from this reaction have been reported.

Neurological

An acute, reversible primarily peripheral sensory neuropathy of early onset, occurring within hours or one to two days of dosing, resolves within 14 days, and frequently recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paraesthesia, dysaesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study subjects who received oxaliplatin with infusional 5-FU/LV. In any individual cycle acute neurotoxicity was observed in approximately 30% of subjects. Ice (stomatitis prophylaxis) should be avoided during the infusion of oxaliplatin because cold temperature can exacerbate acute neurological symptoms.

An acute syndrome of pharyngolaryngeal dysaesthesia seen in 1-2% of subjects is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing).

A persistent (> 14 days), primarily peripheral, sensory neuropathy that is usually characterized by paraesthesias, dysaesthesias, hypoaesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g. writing, buttoning, swallowing, and proprioception-related ambulatory impairment). These forms of neuropathy occurred in 48% of the study subjects receiving oxaliplatin with infusional 5-FU/LV. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the subjects (80%) who developed grade 3 persistent neuropathy progressed from prior grade 1 or 2 events. These symptoms improve in most subjects upon discontinuation of oxaliplatin.

Pulmonary

Oxaliplatin has been associated with pulmonary fibrosis (0.7% of study subjects), which may be fatal. In case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Pregnancy and Lactation

To date there is no available information on safety of use in pregnant women. Based on pre-clinical findings, oxaliplatin is likely to be lethal and/or teratogenic to the human foetus at the recommended therapeutic dose, and is consequently not recommended during pregnancy, and subjects becoming pregnant during the study should discontinue oxaliplatin immediately. Excretion in breast milk has not been studied. Breast-feeding is contraindicated during oxaliplatin therapy.

Veno-occlusive Disease

Veno-occlusive disease, also known as sinusoidal obstruction syndrome, is a form of toxic liver injury characterized clinically by the development of hepatomegaly, ascites, and jaundice and histologically by diffuse damage in the centrilobular zone of the liver. Sequelae of this event include hepatomegaly, splenomegaly, portal hypertension, and oesophageal varices. The incidence of veno-occlusive disease associated with oxaliplatin usage is considered to be very rare. Standard clinical practice should be used for evaluation of veno-occlusive disease, including observation of liver and spleen size, history of or actual gastrointestinal bleeding, reversal of portal blood flow visualized by ultrasound, and possibly the development of oesophageal varices and bleeding or jaundice. Subjects who develop clinically significant veno-occlusive disease should discontinue oxaliplatin therapy.

Haematological

Oxaliplatin myelotoxicity is modest. The addition of oxaliplatin to 5-FU-based regimens is associated with increased incidence of low grades of thrombocytopenia, anaemia, and grade 3-4 neutropenia. Neutropenia is more frequent and severe with the use of bolus plus infusional bimonthly regimes of 5-FU/LV.

Gastrointestinal

Nausea, vomiting, constipation, diarrhoea, and stomatitis can occur. The incidence of severe diarrhoea seems to increase when oxaliplatin is added to the bolus daily times 5 regimen of 5-FU/LV. Subjects receiving 5-FU/LV containing regimens may experience bowel wall abnormalities (characterized by ileus and/or enterocolitis and thickening or ulceration of the small and/or large bowel) and infection (with or without neutropenia) requiring prolonged hospitalization.

Rash

Hand-foot skin reaction and injection site reactions have been seen.

Fever

Fever during infusion of oxaliplatin has been reported. Fever has been associated with the use of oxaliplatin.

Infection

May occur with normal ANC or unknown ANC.

Hepatic

Alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase (GGT), ALAT (SGPT), ASAT (SGOT) have all been reported to be elevated.

Renal

Subjects may experience some degree of elevation of serum creatinine. The incidence of grade 3/4 elevations is about 1% in previously treated subjects.

Cardiovascular

There has been reported incidence of thromboembolism.

Contraindications

Oxaliplatin is contraindicated in pregnant or breast-feeding women and in subjects

- with a known allergy against oxaliplatin or other platinum compounds

- with impaired bone marrow function
- with preexisting peripheral neuropathy
- with severe renal impairment.

For complete prescribing information, please refer to the SmPC (app. 6).

5.2.5 Modifications of therapy and dosage

5.2.5.1 General remarks

The handling of a combination of irradiation and hyperthermia with 5-FU and oxaliplatin is especially demanding with respect to toxicity and required dose adjustment, when compared to established dosing recommendations in case of adjuvant or palliative chemotherapy only:

1. There may be overlapping toxicities of the modalities,
2. Typical toxicities related to 5-FU infusion (hand-foot syndrome) and oxaliplatin (neuropathy) are expected to be rare and/or low intensity events during the therapy course of this protocol, as the cumulative doses in the combined modality course are rather low,
3. The main strategy of treatment adjustment, if required, should focus on the avoidance of treatment interruptions or premature termination.

The acute and protracted toxicity will be categorized and graded according to the NCI Common Terminology Criteria for Adverse Events, v 3.0 (CTC AE) (cf. appendix 3). In case of toxicities without severe or life-threatening sequelae (e.g. alopecia), the treatment should not be modified. If several toxicities of the same type occur simultaneously, the most pronounced of the proposed treatment adjustment procedure should be applied. When, according to the investigator's judgment, an adverse effect is exclusively related to one modality or drug (e.g. hand-foot syndrome due to protracted 5-FU infusion, neurotoxicity due to oxaliplatin), the dosage/intensity of the other drugs/modalities does not have to be modified.

In case of a dose necessary dose reduction, the reduced dosage will be administered during the whole remaining protocol treatment procedure. A subsequent re-escalation is not allowed. If, due to toxicity, the treatment has to be delayed for more than two weeks, the patient goes off protocol treatment and the end-of-treatment document page is reported.

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

5.2.5.2 Specific modifications

It is decisive for dose modification, whether the toxicities occur

1. on the day of the oxaliplatin iv. application or
2. during the 5-FU infusion or
3. on another day of the treatment course

If a toxicity occurred during the interval between the chemotherapy courses, the drug dose in the subsequent course will be adapted according to the following table:

CTC grade	1	2	3	4
WBC	100%	100%	5-FU: 75%	5-FU: 75% L-OHP: 75%
Platelets	100%	100%	5-FU: 75%	5-FU: 75% L-OHP: 75%
Mucositis	100%	100%	5-FU: 75%	5-FU: 75% L-OHP: 75%
Diarrhea	100%	100%	5-FU: 75%	5-FU: 75% L-OHP: 75%
Skin	100%	100%	5-FU: 75%	Off treatment

If one of the following toxicity findings is still present on the day of the next chemotherapy administration:

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

therapy has to be delayed for at least one week, and started when WBC have risen to > 3000/µl and platelets to > 100.000/µl and gastrointestinal toxicities have resolved. If necessary, a delay for a second week is allowed.

The following dose adjustments have to be undertaken in case of neurotoxicity caused by oxaliplatin:

	Duration of toxicity		
	1-7 days	> 7 days	Persisiting durimng the chemotherapy interval
Cold related dysaesthesia	No change	No change	No change
Paraesthesia	No change	No change	Reduce by 25%
Paraesthesia with pain	No change	Reduce by 25%	stop L-OHP continue 5-FU
Paraesthesia with functional impairment	No change	Reduce by 50%	stop L-OHP continue 5-FU

In a small number of patients a special form of acute neuropathy, laryngopharyngeal dysaesthesia syndrome, may occur with a subjective feeling of dysphagia and dyspnoea but without objective signs of airway obstruction. This syndrome is not life-threatening and rapidly reversible without any treatment. During the following cycles the duration of infusion should be prolonged to 6 hours.

The specific neurotoxicity caused by oxaliplatin is recorded according to the following scale developed by Wassermann et al.:

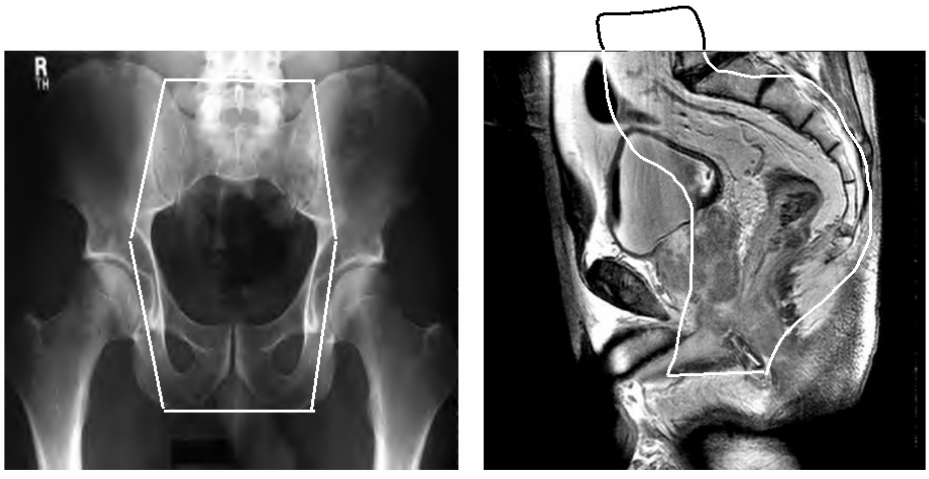
Grade 1	Paraesthesia/Dysaesthesia ≤ 7 days
Grade 2	Paraesthesia/Dysaesthesia 8-14 days
Grade 3	Paraesthesia/Dysaesthesia > 14 days
Grade 4	Paraesthesia/Dysaesthesia with functional impairment

5.3 RADIOTHERAPY

5.3.1 Description

No prior pelvic irradiation:

Patients undergo radiotherapy once daily, 5 days a week, for 5 weeks. Patients receive 45 Gy (25 x 1.8 Gy) to the pelvis (ICRU-report 50). The pelvic radiotherapy uses a three or four field box technique and at least 6 MV photon beams. The field borders for pelvic irradiation are confined as follows:



Patients with tumors that are considered as not resectable after 45 Gy receive a 3D-conformal boost to the gross tumor volume with a security margin of 1-2 cm in every direction to a total dose of 59.8 Gy, at least. Patients with tumors that are considered as resectable receive surgery in curative intention 4-6 weeks after completion of chemoradiation.

Prior pelvic irradiation:

Patients undergo 3D-conformal radiotherapy once daily, 5 days a week, for 5 weeks. Patients receive 45 Gy (25 x 1.8 Gy) to the gross tumor volume with a security margin of 1-2 cm in each direction (ICRU-report 50). Radiotherapy uses 6 MV photon beams, at least.

Patients with tumors that are considered as not resectable after 45 Gy receive a 3D-conformal boost to the gross tumor volume with a security margin of 1-2 cm in every direction. The total dose is left to the discretion of the local radiotherapist. Patients with tumors that are considered as resectable receive surgery in curative intention 4-6 weeks after completion of chemoradiation.

5.3.2 Modifications in case of toxicity

In case of acute diarrhea or hemorrhagic cystitis grade 4 during treatment, radiotherapy will be withheld until resolution of symptoms. When radiotherapy is withheld, chemotherapy and hyperthermia will not be delivered. RT will also be withheld for WBC <1.0 x 10^9/l, neutrophil count < 0.3 x 10^9/l and/or platelet count < 20 x 10^9/l. If the treatment delay exceeds two weeks, the patient goes off protocol treatment and the end-of-treatment document page is reported.

5.4 DEEP REGIONAL HYPERTHERMIA

5.4.1 Description

Hyperthermia is scheduled twice weekly during the time of external radiotherapy and started within one hour before or after irradiation to a total of 10 treatments. The interval between two RHT-treatments has to be a minimum of 72 hours. Thermometry probes have to be positioned in the rectum (if accessible), the bladder, the vagina and the rima ani for continuous thermometry and thermal mapping of tumor-related temperatures. Therapeutic time starts when the tumor-related temperature in the rectum reached a minimum of 41.5°C or 30 min after enabling power. Therapeutic time is scheduled to be 60 min, the maximum total duration should not exceed 90 min.

Maximum bladder and vagina temperatures should not exceed 43°C. In the event that bladder temperature exceeds 43˚C irrigation of the bladder with a cool saline solution may be carried out to reduce bladder temperature without necessarily decreasing power. Systemic body temperature (measured orally) should not exceed 39°C. In the event of systemic temperature rising above this level, cooling of the patient should be attempted with fans, cool water, etc. before decreasing power.

Power should be adjusted for heart rate and/or blood pressure changes at the discretion of the individual institution.

5.4.2 Modifications in case of toxicity

In case of small volume first-, second-, or third-degree burns (<3 cm in greatest dimension) generally no adjustment is necessary. Therapy may be continued at the discretion of the attending physician unless pain is prohibitive. In the case of subcutaneous burns (i.e. subcutaneous nodules or fat necrosis) therapy may generally be continued unless prohibitive pain dictates discontinuance at the discretion of the attending physician.

Radiotherapy or chemotherapy will not be withheld in the event that hyperthermia has to be withheld. In the event that chemotherapy must be withheld, radiotherapy and hyperthermia will not necessarily be withheld unless the specific criteria for dose modification are met. No hyperthermia will be delivered after the conclusion of radiotherapy, even if one or more hyperthermia treatments were skipped.

5.5 SURGICAL THERAPY

4-6 weeks after chemoradiation, tumour resection should be performed if possible and if no contraindications are present. Contraindications may be infiltration of the sacral vertebras 1 and 2 or infiltration of the basal pelvic muscles. The definite decision on further surgical treatment is left to the discretion of the local surgeon.

All surgical procedures should be performed according to the local standards of the invstigator's institution, according to established guidelines and recommendations. Surgery is not considered as an integral part of the experimental study treatment.

5.6 CONCOMITANT AND SUPPORTIVE TREATMENT

5.6.1 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
- initial prophylactic use of G-CSF, GM-CSF and other growth factors

Concomitant medication, which is relevant for the study assessments, have 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.

5.6.2 Treatment of nausea/vomiting

For acute nausea and vomiting, a 5-HT3 antagonist with corticosteroids prior to infusion would be considered standard premedication for oxaliplatin. For delayed nausea and vomiting, an oral 5-HT3 antagonist is the first option; metoclopramide, alizapride and prochlorperazine may be also used.

5.6.3 Treatment of diarrhea

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, up to a maximum treatment duration of 48 hours. 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 or prolonged diarrhea (> 48 h despite loperamide treatment) **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).

5.6.4 Prevention and treatment of neutropenia

In case of severe neutropenia patients undergo a high risk of developing infections and/or febrile neutropenia, especially if diarrhea occurs simultaneously. As soon as an asymptomatic grade 4 neutropenia or a febrile neutropenia (grade 3 or 4) is recorded, the dose of future chemotherapy applications has to be modified (cf. section 5.2).

Prophylactic treatment with antibiotics is not recommended, even in case of grade 4 neutropenia (without fever or diarrhea), but the decision is up to the local investigator's preference. Prophylactic hematopoietic growth factors (i.e., G- or GM-CSF) are not recommended, but secondary prophylaxis after a previous episode of neutropenia is up to the discretion of the investigator. 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.

5.7 EMERGENCY MANAGEMENT

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

Dr. med. Oliver J. Ott (LKP)
Univ. Hospital Erlangen
Dept. of Radiation Oncology
Universitätsstraße 27
D-91054 Erlangen
Germany
Phone: +49 9131 8532935
Fax: +49 9131 8532969
Email: oliver.ott@strahlen.imed.uni-erlangen.de

Serious adverse events or reactions (cf. section 6.7.3 and 6.7.4), observed during the conduct of the study, have to be reported to the coordinating investigator/sponsor within 24 hours. A specific SAE form has to be filled.

5.8 PREMATURE WITHDRAWAL OF AN INDIVIDUAL SUBJECT

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

- disease progression,
- development of unacceptable toxicity
- 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.

5.9 PREMATURE STUDY TERMINATION BY THE SPONSOR/COORDINATING INVESTIGATOR

At any time, the sponsor/coordinating investigator of the study 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, administrative or legal reasons (including insufficient patient recruitment), especially if severe and/or frequent adverse events occur, requiring a new risk/benefit evaluation.

6 STUDY ASSESSMENTS AND CRITERIA OF EVALUATION

6.1 OVERVIEW / SCHEDULE OF STUDY ASSESSMENTS

STUDY PARAMETERS	pre-study	day 1, 9, 16, 23, 30	on day 9 + 23, additionally	end of treat-ment, day 35	post-surgery (if possible)	follow-up[6]
Informed consent	X[1]					
History	X[1]					
Physical exam	X[2]	X		X	X	X
Vital Signs	X[2]	X		X	X	
Neurological exam	X[2]		X	X		X
Height	X[2]					
Body weight	X[2]	X				
Performance status	X[2]			X	X	X
ECG	X[1]			X[5]		
Pregnancy test	X[1,4]					
CBC/differential blood count[7]	X[2]	X		X		
Serum chemistry[8]	X[2]	X		X		
CEA	X[2]					
Toxicity/symptoms (NCI CTC)	X[2]	X		X	X	X
Tumor assessment	X[3]			X	X	X
Chest X ray	X[3]			X[5]		X[5]
Endosonography	X[3]					
Rektosigmoidosc./ coloscopy	X[3]			X		
CT of abdomen	X[3]			X		X
Pathology	X[3]				X	

1. Within 14 days prior to the start of therapy.
2. Within 7 days prior to the start of therapy.
3. Within 21 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, thereafter every 6 months for 3 additional years
7. Hb, WBC, granulocytes, platelets
8. Sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, LDH, alk. phosphatase, total protein, albumin.

6.2 ASSESSMENTS AT RECRUITMENT

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

- Signed written informed consent.
- Complete medical history including dates and description of initial diagnosis of rectal cancer, pre-treatment, documentation and measurement of all measurable and/or non-measurable lesions, tumor related symptoms, relevant concurrent illnesses and relevant concomitant medication.
- Physical examination including: weight, height, WHO performance status (appendix 2), and complete neurological examination within 7 days prior to treatment.
- Vital signs: blood pressure, pulse rate and oral temperature within 7 days prior to treatment.
- Residual toxicities from prior therapies should be recorded using the NCI Common Toxicity Criteria (appendix 3).
- 12 lead ECG.
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count.
- Clinical chemistry: Sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, LDH, alk. phosphatase, total protein, albumin
- Tumor marker (CEA).
- Urine or serum HCG if patient is of childbearing potential.
- Chest X ray within three weeks prior to treatment.
- Endosonography within three weeks prior to treatment.
- Rectosigmoidoscopy/coloscopy within three weeks prior to treatment.
- CT scan of the abdomen

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, 9, 16, 23, 30 of radiochemotherapy:

- Physical examination, vital signs, performance status
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count.
- Clinical chemistry: Sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, LDH, alk. phosphatase, total protein, albumin
- Toxicity assessment according to NCI CTC (cf. appendix 3)

In addition, on day 9 and 23:

- Neurological examination

At the end of radiochemotherapy (day 35):

- Physical examination, vital signs, performance status
- Neurological examination
- 12 lead ECG (if clinically indicated).
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count.
- Clinical chemistry: Sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, LDH, alk. phosphatase, total protein, albumin
- Toxicity assessment according to NCI CTC (cf. appendix 3)
- Tumor assessment by imaging techniques, corresponding to those used at baseline. Additional tumor assessments, if clinically indicated.

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

6.4 DOCUMENTATION AFTER SURGERY

- Physical examination, vital signs, performance status
- Toxicity assessment according to NCI CTC (cf. appendix 3), especially with respect to post-surgical complications
- Additional tumor assessments, if clinically indicated.
- Pathological description of surgical results and specimen

6.5 FOLLOW-UP DOCUMENTATION

Follow-up documentation is performed in order to assess the secondary efficacy objectives of progression-free and overall survival. The follow-up programme corresponds to the guidelines of the German Cancer Society.

- Physical examination, vital signs, performance status
- Neurological examination
- Toxicity assessment according to NCI CTC (cf. appendix 3), especially with respect to late complications
- Tumor assessments, including chest X-ray (if clinically indicated), and CT of the abdomen

6.6 CRITERIA FOR EFFICACY EVALUATION

6.6.1 Tumor evaluations

Tumor measurements are to be made using the same method (e.g. physical examination, sonography, X-ray, CT scan) at each assessment. All measurable and evaluable disease should be followed until disease progression. If a patient has clinical signs of progression, then tumor evaluation can take place at that time.

All tumor evaluation is performed according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria and standards (appendix 1). Confirmation of declared remissions (CR or PR) must be performed no earlier than 28 days after the original declaration of response.

6.6.2 Local progression-free survival

Local progression-free survival will be defined as the time from the initial dose of radiochemotherapy to the time of locoregional disease progression or relapse (according to the TNM system) or death, or to the date of last assessment without any such event (censored observation).

6.6.3 Distant metastasis-free survival

Distant metastasis-free survival will be defined as the time from the initial dose of radiochemotherapy to the time of distant metastasis detection or death, or to the date of last assessment without any such event (censored observation).

6.6.4 Overall survival

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

6.7 CRITERIA FOR SAFETY EVALUATION

6.7.1 Dose-limiting toxicity (DLT)

The following adverse reactions are defined as dose-limiting toxicity in the context of the **primary objective** of the trial to determine the feasibility rate (cf. section 7.2):

- Leukopenia or neutropenia of severity grade 3 or 4 with complications such as fever (> 38,5°C) or infection, or with a duration of > 7 days
- Thrombocytopenia of grade 3 or 4
- Non-hematological toxicity of grade 3 or 4 (except for nausea)
- Each toxicity leading to permanent discontinuation of at least one of the drugs or other treatment modalities, except for hyperthermia, if more than 60% of the scheduled applications occurred, or a delay of treatment of more than 3 weeks

6.7.2 Toxicity / adverse events (AE)

Adverse events (AE):

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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. 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 noxious 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.

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 6.7.3.

All adverse events and toxicities are recorded continuously and reported in the Toxicity Form of the CRF (cf. section 6.7.4 for details).

6.7.3 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.

Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or malignant tumors when they are histologically different from the primary tumor.

SUSARs (Suspected Unexpected Serious Adverse Reaction) represent Serious Adverse Events related to a study drug (=adverse reactions), considered “unexpected” with regard to the valid investigator's brochure or SmPC for the respective drug.

6.7.4 Methods of recording and assessing adverse events

All AEs must be documented with its NCI CTC severity grade 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 6.7.5 for exemptions).

The following detailed information must be recorded for each **serious** adverse event in the CRF:

- A description of the AE in medical terms, not as reported by the subject
- The date of onset (start date)
- The time of onset in case event started at the day of study drug administration (start time)
- The date of recovery (stop date)

- The time of recovery in case event stopped at the day of study drug administration (stop time)
- The grade as assessed by the investigator according to the definitions in NCI-CTC (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:

  Recovered with sequelae.

  Recovered without sequelae.

  Ongoing, no therapy.

  Ongoing, therapy.

  Died.

  Change in toxicity grade/severity.
- It must be indicated whether the SAE is the leading event, 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 for 30 days after the last dose of study treatment. Serious adverse events occurring more than 30 days 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.

6.7.5 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 6.7.3) 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 investigator-sponsor **within 24 hours** by phone or fax:

Dr. med. Oliver J. Ott (LKP)
Univ. Hospital Erlangen
Dept. of Radiation Oncology
Universitätsstraße 27
D-91054 Erlangen
Germany
Phone: +49 9131 8532935
Fax: +49 9131 8532969
Email: oliver.ott@strahlen.imed.uni-erlangen.de

The immediate report by the investigator to the investigator-sponsor 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.

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 investigator-sponsor of the study 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 comitee(s), according to §12, Abs. 6 and § 13, Abs. 1 to 7 of GCP-V, are fulfilled.

The sponsor is obliged to inform the participating investigators about SUSARs (cf. section 6.7.3 for definition), according to the German regulations (§11, Abs. 2 and 3 of GCP-V).

Events not to be treated as SAEs:

Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from expedited reporting on a SAE report form (exemptions allowed according to §12, Abs. 4, GCP-V):

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

6.7.6 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 study visits. It is the responsibility of the investigator that any necessary additional therapeutic measures and follow-up procedures are performed.

6.7.7 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 computer database system. 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.

The following software systems will be used:

S-PLUS by Insightful Corp., Seattle, USA

Report/Testimate/N/Nsurv der Fa. IDV, Gauting

VisualFoxpro für Windows von der Fa. Microsoft, Redmond, USA

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 I/II study which aims at estimating the feasibility of the combined modality regimen consisting of chemoradiation including 5-FU/oxaliplatin and deep regional hyperthermia. The feasibility rate, i.e. the rate of patients without DLT (according to the definition in section XXX) *or* premature radiochemotherapy treatment withdrawal *or* hyperthermia delivery < 80%, is chosen as primary efficacy endpoint.

The estimation of the feasibility rate is to be based on an explorative pilot study, since immediate embarking on a large scale comparative efficacy trial would not be acceptable from the point of view of resources. Moreover, this would induce ethical objections, as it does not seem to be justifiable to expose a large number of patients to an experimental approach without any exploratory indications of an improved risk-benefit ratio.

7.2.2 Sample size calculation

The main objective of the trial is to assess, whether radiochemotherapy plus hyperthermia shows a promising feasibility profile in the treatment of locally recurrent rectal cancer. The primary endpoint is the feasibility rate as defined in section 7.2.1.

Conventional empirical phase I study designs in clinical oncology assume, that an antineoplastic treatment is not feasible, if an unacceptable toxicity occurs in more than 1 out of 3 or 4 patients; however, the occurrence of dose limiting toxicities (DLT) in 1/6 is accepted[32,33,34,35]. This leads to the conclusion that the limit of acceptance is considered to be around 20% in medical cancer treatment.

In order to (from an ethical point-of-view) prevent to treat an unnecessarily high number of patients with a treatment regimen that is practically not feasible, a two-stage design according to SIMON (1989) will be applied. This allows for the termination of the study with a relatively low patient number in case of a definitely not acceptable feasibility rate. If this first step is passed without termination, further recruitment occurs in a second stage, in order to be able to ascertain a promising level of feasibility, hence qualifying the experimental treatment for further evaluation or application.

In summary, the trial design is based on the following assumptions:

- The experimental therapy would be rated as unacceptable, if the actual feasibility rate (= 1 – withdrawal/DLT rate) was 70 % or lower.
- On the other hand, the multimodal regimen would be considered to be a promising candidate for further development (e.g. in a phase III trial), if the true feasibility rate amounted to 85% or more.
- Probability to accept the experimental therapy as well tolerable, in spite of a *true* feasibility rate of < 70% (i.e. withdrawal/DLT rate > 30%): 5% (type I error)
- Probability to reject the experimental therapy as not sufficiently feasible (<70%), although the *true* feasibility rate is promising (> 85%): 20% (type II error, corresponding to a power of 80%).

According to these parameters, and using the variant out of the class of optimal two-stage designs by SIMON (1989) that leads to the lowest expected number of patients required in case of true non-feasibility, **n = 19 patients** evaluable for feasibility have to be recruited in the first stage. The combination will be rejected, if five or more of these patients fulfil the criterion of non-feasibility. In the second step, further patients will be recruited up to a total number of **59 evaluable cases**. The final conclusion of the trial will depend on the definite feasibility rate (and its confidence interval), the

achieved level of treatment delivery (especially, the number of hyperthermia applications) as well as the complete information on type, frequency and severity of toxicities.

The precision of the estimation of the feasibility rate in the respective arms/strata is provided by confidence intervals in the following table, for different actual feasibility rate findings:

Feasibility rate	exact 90% confidence interval
41/59 (≈70%)	58 ... 79 %
47/59 (80%)	69 ... 88 %
53/59 (90%)	81 ... 95 %

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.

If a patient goes off treatment during the first two cycles for clearly other reasons than toxicity, he will not be included in the feasibility rate finding process and has to be replaced.

All patients having received at least one application of 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 p values are calculated (e.g. in subgroup comparisons or across treatment arms), they 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.

Feasibility, toxicity, response and event rates at pre-specified time points are calculated, providing confidence intervals. In case of comparison between patient groups, these rates will be analyzed by Fisher´s exact test, χ^2 test or Mantel-Haenszel test (or trend test according to COCHRAN/ARMITAGE), respectively.

Event related data like progression-free or overall survival will be estimated by the product limit method[36] (KAPLAN and MEIER, 1958) and compared using the logrank test. If the Peto logrank test[37] (PETO, 1972, 1977) is not appropriate because of violation of the proportional hazard assumption (HAYBITTLE 1988), Gehan's generalization of the Wilcoxon rank sum test for censored data (GEHAN 1965) will be applied, preferably in its modification by PETO (1972) and PRENTICE (1978). If appropriate, prognostic strata will be taken into account (PETO, 1977).

7.2.5 Interim and final analyses

As described and justified in 7.2.2, an interim analysis is performed, when 10 patients are evaluable for feasibility.

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 as well as after completion and/or correction of all case report forms. An additional analysis on long-term results will be performed 5 years later.

8 STUDY DOCUMENTATION AND ARCHIVING

8.1 DOCUMENTATION AND INFORMATION FLOW

All patient-related data are recorded in a pseudonomized 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, appendix 8) 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.

Version to be corrected:

1	2	1	3	0	3
day		month		year	

corrected version:

2 date, initials

1	2	1	~~3~~	0	3
day		month		year	

- Please write legibly and use printing letters

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/coordinating investigator(s) will take care of the financing/funding of the study. The “Deutsche Krebshilfe” is the main funding source.

10 USE OF INFORMATION AND PUBLICATION

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.

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.

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.

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, 12. Novelle, 2004), "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 9th August 2004. The coordinating investigator has at least two years of experience in clinical trials on medicinal products. He is at the same time sponsor of the study with respect to GCP regulations (according to article 7 of the EC Commission Directive 2005/28/EC), since 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 Assemblies in Tokyo, Japan, October 1975, Venice, Italy, October 1983, Hong Kong, September 1989, Somerset West, South Africa, October 1996, and Edinburgh, Scotland, 2000. The declaration is included as appendix 7.

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” (Appendix 4), 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 (Appendix 5) 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. Evaluation of response efficacy is performed according to RECIST standards.

11.4.2 Monitoring / source data verification

The study will be monitored externally by regular site visits and telephone calls to the investigator by authorized personnel of the principal investigator. 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. In addition, the monitor should review original patient records, 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

Prior to start 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 "Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM) and/or 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/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/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 investigator(s) 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.

11.8 SUBJECT INSURANCE

An indemnity insurance will be contracted for the trial subjects with XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX, in accordance with § 40, Abs. 1, Nr.8 and Abs. 3 AMG. 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.

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