Multi-institutional Phase I/II Study: Neoadjuvant chemoradiation with 5-FU (or capecitabine) and oxaliplatin combined with deep regional hyperthermia in locally advanced or recurrent rectal cancer (HyRec Trial) - ESH0201107/001 Study Protocol -

Final Report

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Medizinischen Fakultät der Universität Erlangen-Nürnberg)

Investigational drugs	5-Fluorouracil, Capecitabine, Oxaliplatin, Deep Regional Hyperthermia, Radiotherapy
Sponsor	Universitätsklinikum Erlangen, Strahlenklinik, insoweit handelnd für den Freistaat Bayern, vertreten durch den Dekan der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg
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1	**Name of Sponsor/Company**
	Universitätsklinikum Erlangen, Strahlenklinik, insoweit handelnd für den Freistaat Bayern, vertreten durch den Dekan der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg
2	**Name of Finished Product**
	5-Fluorouracil medac, Xeloda, Oxaliplatin Hospira All brands of the active substances were allowed in the study.
3	**Name of Active Substance**
	5-Fluorouracil, Capecitabine, Oxaliplatin, Deep Regional Hyperthermia, Radiotherapy
4	**Individual Study Table: Referring to Part of the Dossier (Volume, Page)** **Anmerkung: Diese Angabe ist nur bei Einreichung in Zusammenhang mit einem Zulassungsdossier erforderlich**
	Not applicable
5	**Title of Study** **Anmerkung: Es muss klar hervorgehen, dass die letzte Protokollversion einschließlich aller Amendments gemeint ist, die Amendments sind anzugeben und zu identifizieren**
	Multi-institutional Phase I/II Study: Neoadjuvant chemoradiation with 5-FU (or capecitabine) and oxaliplatin combined with deep regional hyperthermia in locally advanced or recurrent rectal cancer (HyRec Trial) - ESHO201107/001 Study Protocol - v4.0 Previous Protocol Versions/Amendments: • ESHO201107/001 v. 3.0 – 11.04.2012 First Submission • ESHO201107/001 v. 3.1 – 30.07.2012 First Approval (Amendment 1) • ESHO201107/001 v. 3.2 – 14.12.2012 Amendment 2 • ESHO201107/001 v. 4.0 – 16.03.2016 Amendment 3 Definition of a new primary efficacy endpoint after completion of feasibility analysis End of Recruitment 01.11.2019 End of Trial (last patient last visit): 28.11.2023
6	**Investigators**
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8	**Publication (reference)**	
	Ott OJ, Gani C, Lindner LH, Schmidt M, Lamprecht U, Abdel-Rahman S, Hinke A, Weissmann T, Hartmann A, Issels RD, Zips D, Belka C, Grützmann R, Fietkau R. **Neoadjuvant Chemoradiation Combined with Regional Hyperthermia in Locally Advanced or Recurrent Rectal Cancer.** *Cancers (Basel) 2021;13:1279.*	
9	**Studied period (years): date of first enrolment, date of last completed** **Anmerkung: Hier sollen auch Studienunterbrechungen und vorzeitige Studienbeendigungen/Studienabbrüche unter Angabe der Gründe aufgeführt werden**	
	First patient in: 02.11.2012 Last patient out of therapy: 31.10.2018 End of Follow up: 28.11.2023 No interruptions of the trial were made.	
10	**Phase of development**	
	Phase II trial	
11	**Objective**	
	Main question Primary objective of the study is to decide upon the feasibility of the combined modality regimen consisting of chemoradiation including 5-FU (or its prodrug capecitabine)/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.	

	Amendment 2016: To decide upon the response rate (especially pCR rate) of a multimodal regimen consisting of radiochemotherapy and hyperthermia.
12	**Methodology**
	Multicenter, open-label phase 2 study Between 2012 and 2018, 111 patients with UICC stage IIB-IV or any locally recurrent rectal cancer were included (HyRec-Trial, ClinicalTrials.gov Identifier: NCT01716949). Patients received radiotherapy with concurrent 5-Fluororuracil/Capecitabine and Oxaliplatin, and deep regional hyperthermia. Stage 1 feasibility analysis evaluated dose-limiting toxicities after 19 patients, stage 2 after 59 evaluable patients. Amendment 2016: Analysis of the pCR rate was based on histopathological reports.
13	**Number of patients (planned and analysed)**
	Initially planned: 59 Amendment 2016: a total of 110 Enrolled: 111 Analysed: 105
14	**Diagnosis and main criteria for inclusion**
	Diagnosis: Histologically confirmed, locally advanced or recurrent (any recurrence of tumor within the lesser pelvis; resectable or non-resectable) adenocarcinoma of the rectum (UICC stages IIB - IV). **Main criteria for inclusion:** Histologically confirmed, locally advanced or recurrent (any recurrence of tumor within the lesser pelvis; resectable or non-resectable) or locally advanced adenocarcinoma of the rectum (UICC stage IIB-IV); distant oligo-metastases may be present. ECOG-performance status < 2 Age ≥ 18 Considered fit for oxaliplatin and 5-FU-containing combination chemotherapy Written informed consent for the participation in the clinical trial
15	**Test product, dose and mode of administration, batch number**
	The IMPs are only defined only by active substance – all brands are allowed in the study. Radiotherapy was applied using linear accelerators to deliver megavoltage external-beam irradiation to the primary and lymphatics or the local recurrence. For treatment planning, either 3D-conformal or intensity-modulated radiotherapy (IMRT) techniques were applied with 6 MV photon beams, at least. Dose was specified according to the International Commission on Radiation Units (ICRU) Reports 50 and 62. Regarding LARC, the planning target volume

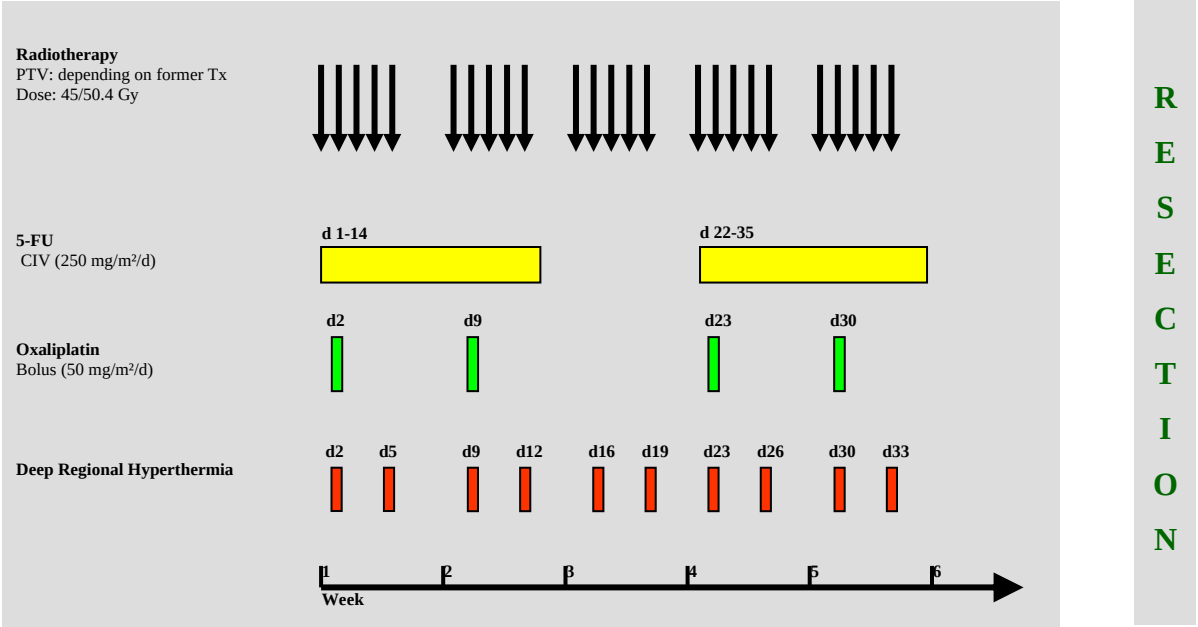
(PTV) encompassed the gross tumor volume (GTV) and the pelvic lymphatics (CTV) with an additional appropriate safety margin of 3–5 mm for intrafractional motion and daily interfractional positioning errors. Radiotherapy was administered once daily, five days a week, up to a total dose of 50.4 Gy (28 × 1.8 Gy). In cases of LRRC without prior pelvic irradiation, PTV definition and dose followed the same standards as for LARC. For patients with LRRC and prior pelvic radiotherapy in their histories, the target volume consisted of the GTV with a safety margin of 1–2 cm in each of six directions for covering both CTV and PTV with respect to non-infiltrated anatomical borders. These patients received daily radiotherapy fractions up to a total dose of 45 Gy (25 × 1.8 Gy). Further boost irradiation was not performed in any patient.

Patients received simultaneous chemotherapy with 5-FU and Oxaliplatin. 5-FU was applied with 250 mg/m2/d as continuous intravenous infusion on days 1–14 and 22–35. Oxaliplatin with 50 mg/m2 was given as intravenous bolus infusion diluted in 500 mL glucose 5% over two hours on days 2, 9, 23, and 30. Alternatively, 5-FU could have been replaced by its prodrug Capecitabine with oral doses of 1650 mg/m2/d on days 1–14 and 22–35, given in two separate doses of 825 mg/m2, in the morning and evening.

RHT was applied in accordance with the published guidelines for the use within clinical studies. It was performed with the BSD 2000-3D- and BSD 2000-3D-MR-Hyperthermia SystemsTM (BSD Medical Corporation/Pyrexar, Salt Lake City, UT, USA) using either the SigmaEyeTM, SigmaEye-MRTM, or Sigma60TM applicator, depending on the abdominal diameter of the patient. RHT was given twice weekly and started right before irradiation up to ten treatments. The interval between two RHT treatments was 72 h at least. Thermometry probes were inserted in the rectum, the bladder, the vagina, and the rima ani for continuous thermometry and thermal mapping. Therapeutic time started when the tumor-related temperature in the rectum reached a minimum of 41.5 °C or 30 min after enabling power. Therapeutic time was scheduled to be 60 min, the maximum total duration was limited 90 min. During treatment, patients' cardiac function was continuously monitored by electrocardiogram, and blood pressure and oxygen saturation levels were constantly controlled.

Surgery was performed 4–8 weeks after chemoradiation. All surgical procedures had been performed according to the institutional standards in consideration of contemporary guidelines. Per protocol, surgery was not regarded as an integral part of the tested study regimen.

Flow chart



The baseline assessment included history taking, physical examination, quality of life questionnaire, electrocardiogram, pregnancy test, extensive hematological tests, baseline toxicity grading, and staging examinations (histology, chest X-ray, endosonography, rectosigmoideoscopy/coloscopy, abdominal computed tomography). The weekly assessments during therapy included physical examination, hematological tests, and toxicity assessment according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0. Six weeks after chemoradiotherapy (CRT), the weekly assessments were repeated ('the end of treatment visit').

Follow-up examinations were scheduled 3, 6, 12, 18, 24, 36, 48, and 60 months after the end of treatment visit and included histological results, physical examination, and a toxicity assessment according to NCI CTCAE v.4.0 with respect to late complications, and tumor status assessments. Pathological assessment was designed in analogy to our institutional precursor trial and performed in accordance to the applicable national guideline. Minimal requirements for pathological evaluation were histopathologic tumor type, pT-category, pN-category, number of nodes, grading, marginal distances, and R-category. We have previously shown that tumor regression grading (TRG), a semiquantitative assessment of residual tumor cells versus fibroinflammatory tissue in the rectal wall, was able to stratify tumor response to chemoradiation and predict prognosis on an individual-patient. In this study, TRG was recorded prospectively according to Dworak et al. If surgery was performed, the Dworak TRG score was performed by the same pathologist as in the study of Fokas et al. in the majority of the samples. Departmental four-eye-confirmation of pathological results was a standard procedure during the trial.

Considering a proportion of therapy-limiting toxicity or treatment withdrawal of up to 15% as feasible, but a proportion of 30% or more as a clear sign of insufficient feasibility, 59 patients were required to achieve 80% power on a type-one error level of 0.05. The applied two-step design according to Simon allowed for early stopping for futility after an interim analysis of the first 19 patients. Once feasibility was established, the trial was amended in order to obtain evidence for a superior efficacy (pCR rate of 20% or more) in contrast to an assumed pCR of merely 10% after standard therapy, based on historical data [2,4,15,16]. This

required 102 evaluable patients (110 allowing for dropouts) in a single-step phase II design achieving 90% power with a type-one error level of 0.05.

Survival type endpoints were analyzed using the Kaplan–Meier method. The reported p-values are generally two-sided and considered to be explorative.

Procedures

	Baseline	weekly, preferably on d1,8,15,22,29	after RCT weekly	end of treatment[6]	follow up
Informed consent	X[2]				
Medical history	X[2]				
Physical exam	X[3]	X		X	X
Vital signs	X[3]	X		X	
Neurological exam	X[3]	X		X	X
Height	X[3]				
Body weight	X[3]	X		X	
Performance status (ECOG)	X[3]	X		X	X
Quality of life	X[3]	X[7]		X	X
ECG	X[2]	X		X[5]	
Pregnancy test	X[2,4]				
CBC/diff. blood count	X[3]	X	X	X	
Serum chemistry	X[3]	X		X	
Coagulation	X[3]			X	
CEA	X[3]			X	X
Toxicity symptoms	X[3]	X		X	X
Tumor assessment:					
Histology	X				X[11]
Chest X-ray	X[1]			X[5]	X[5]
Endosonography	X[1]			X[5]	X[5]
Rectosigmoidoscopy/ coloscopy	X[1]			X[5]	X[5]
CT of abdomen	X[1]			X[5]	X[5]

1. Within 21 days prior to the start of therapy
2. Within 14 days prior to the start of therapy
3. Within 7 days prior to the start of therapy. Deviations may be discussed with the PI.
4. In case of women with child-bearing potential
5. As clinically indicated; for tumor assessment preferably using the same method at each assessment
6. End of treatment visit will take place approximately 6 weeks after the chemoradiation
7. At the last day of treatment
8. 6, 12, 18, 24, 36, 48, 60 months after the end of therapy
9. Hb, WBC, granulocytes, platelets
10. Sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, gGT, LDH, alk. phosphatase, total protein, albumin
11. Only at first follow up, only if surgery was performed, including regression grading according to Dworak (see appendix)

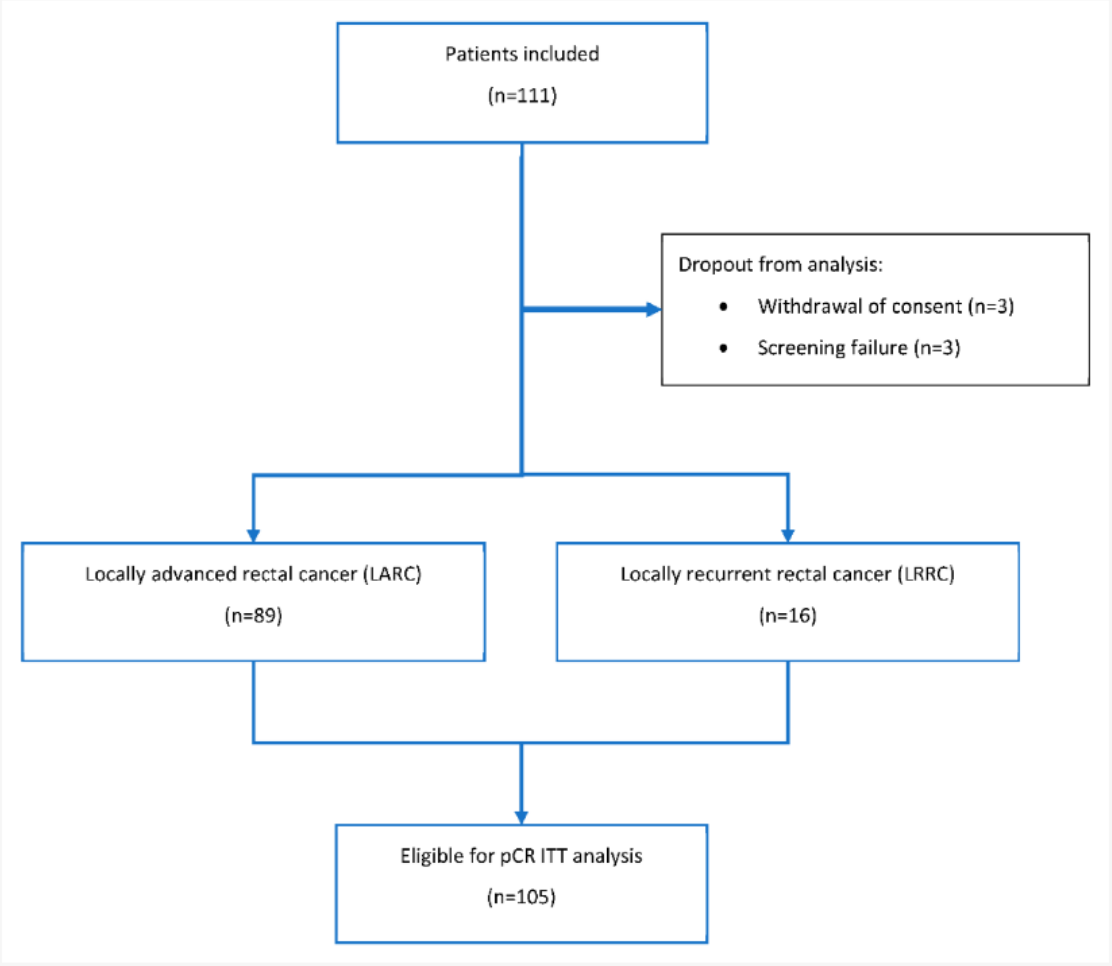
16	**Duration of treatment**
	35-38 days
17	**Reference therapy, dose and mode of administration, batch number**
	Not applicable

18	**Criteria for evaluation Efficacy, Safety**

Efficacy

In an amendment from 2015, the pathologic complete response (pCR) rate was chosen as primary efficacy endpoint. Between 2012 and 2018, 111 patients were included. Because of six dropouts, 105 patients entered the intention-to-treat (ITT) analysis (Figure 1).

Figure 1. Consort diagram. pCR: pathologically confirmed complete remission. ITT: intention-to treat.



Among the 105 patients 71/105 (68%) had no pCR, 11/105 (11%) had no curative surgery, and in three cases (3%) data on the remission status was not available. Six out of eleven cases without curative surgery had a locally recurrent rectal cancer (LRRC), of whom three had a poor response to the neoadjuvant treatment and three others with initially present distant metastasis had progressive metastatic disease. Three of five patients with locally advanced rectal cancer (LARC) without surgery also had progressive distant disease with metastasis present at the time of study inclusion. The two others refused curative surgery because of a clinical complete response. One of them was tumor-free at the last follow-up visit 16 months after study inclusion; the other experienced a local recurrence after a follow-up of 56 months. Regarding the ITT analysis, the proportion with pCR was 20/105 (19%;

90% CI 13.0–26.5) among all patients. Thus, as the lower limit of the one-sided interval excludes the futility threshold of 10% with 95% confidence the study is formally positive with respect to the efficacy endpoint. The pCR rates for patients with LARC and LRRC were 17/89 (19%) and 3/16 (19%), respectively. Excluding the patients with initially diagnosed distant metastases, the proportion with pCR was 19/95 (20%) among all patients, and 16/84 (19%) and 3/11 (27%) for patients with LARC and LRRC, respectively.

Additionally, the tumor regression grading (TRG) according to Dworak was determined, in case curative surgery was performed. The Dworak TRG score considers the response of the primary tumor exclusively. Therefore, one additional patient with LARC (postsurgical TNM staging: ypT0ypN1b) was rated as Dworak TRG 4. The score was not provided by all participating centers' pathologists and available in 72 patients. In the per-protocol analysis of the available cases, a Dworak TRG 4 score was found in 28% (18/64) and 38% (3/8) of the patients with LARC and LRRC, respectively. A combined Dworak 3–4 score as expression of an at-least subtotal complete remission was found in 49/72 (68%) patients. A detailed summary of the Dworak TRG analysis may be found in Table 3.

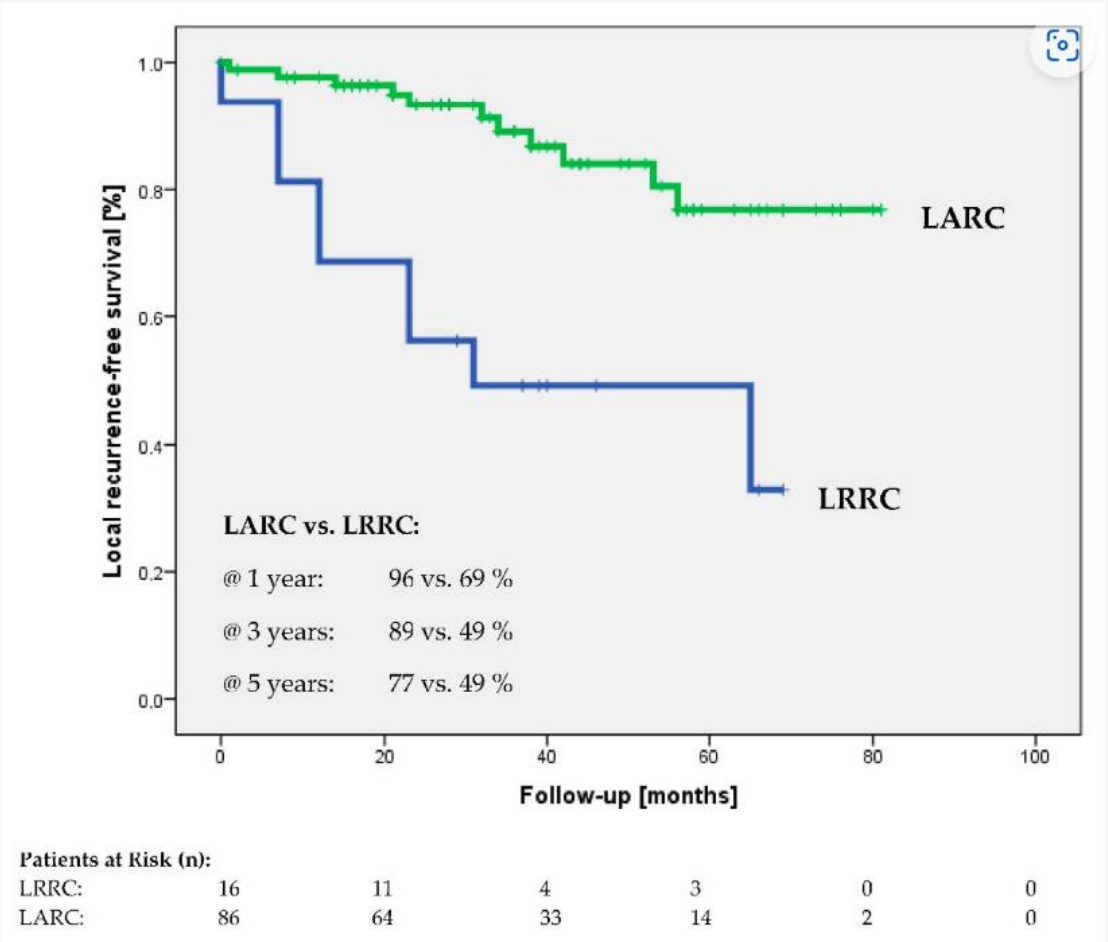
Table 3. Tumor regression grading after curative resection according to Dworak [13].

TRG score	All Patients (*n* = 94)	LARC (*n* = 84)	LRRC (*n* = 10)
Dworak 1	7/94 (7)	5/84 (6)	2/10 (20)
Dworak 2	16/94 (17)	14/84 (17)	2/10 (20)
Dworak 3	28/94 (30)	27/84 (32)	1/10 (10)
Dworak 4	21/94 (22)	18/84 (21)	3/10 (30)
n.a. *	22/94 (23)	20/84 (24)	2/10 (20)

*: the Dworak TRG score was not provided by all participating centers' pathologists. LARC: locally advanced rectal cancer, LRRC: locally recurrent rectal cancer.

Median follow-up for all patients was 34 months (range; 0–81). Five-year overall survival was 75% for the whole group, and 82% vs. 46% for patients with LARC and LRRC. At the time of analysis, 16/105 (15%) patients were dead, 10/105 (9.5%) experienced local recurrence, and 35/105 (33%) had distant metastases. Five-year local recurrence-free and distant metastasis-free survival rates were 77 vs. 49% (see Figure 2) and 60 vs. 41%, respectively. Nine of sixteen patients (56%) died without local control and 15/16 (94%) with distant metastases, and all 16 patients died because of the tumor disease. Regarding LRRC patients only, 7/7 died without local control and 6/7 with distant metastases, and exclusively regarding LARC patients 2/9 died without local control and 9/9 with distant metastases. Disease-specific (DSS) and disease-free survival (DFS) rates differed between the subgroups at five years: 85 vs. 52% and 57 vs. 37%. Among the curatively operated patients, the rates of microscopically complete resections (R0) were 78/79 (99%) and 10/12 (80%) for the LARC and LRRC groups, respectively.

Figure 2. Local recurrence-free survival of locally advanced (LARC) and locally recurrent (LRRC) rectal cancer.



Safety

Radiotherapy was well-tolerated. The mean treatment duration was 38 days (95% confidence interval (CI): 37.0–38.1) for all patients; 38 days (95% CI: 37.5–38.6) and 35 days (95% CI: 33.4–36.2) for patients with LARC and LRRC, respectively. Nearly all patients (104/105) received the scheduled irradiation dose; one LARC patient got a dose reduction to 45 Gy because of diarrhea. Eight percent of the patients (8/105) experienced a radiotherapy delay, mainly because of administrative reasons. The median delay was 2 days (range; 2–6) and 1 day for patients with LARC and LRRC, respectively.

The mean number of RHT fractions was 9.0 (95% CI: 9.0–9.6) treatments in LARC and 9.3 (95% CI: 8.4–10.2) in LRRC. Ninety percent of the patients (94/105) received seven RHT fractions, at least.

Concurrent chemotherapy with 5-FU/Capecitabine and Oxaliplatin was well-tolerated in the vast majority of patients.

Stage 1 Feasibility Analysis

Of the first 20 patients that entered this analysis, one patient dropped out because of a screening failure. Among the remaining 19 patients, 14/19 (74%) had a LARC and 5/19

(26%) a LRRC. No grade 4–5 adverse events occurred. No leukopenia or neutropenia of grade 3 with complications such as fever (>38.5 °C) or infection, or with a duration of >7 days was found. Two patients experienced a non-hematological toxicity of grade 3. In any patient, no toxicity led to permanent discontinuation of at least one of the drugs or other treatment modalities or a delay of treatment of more than three weeks. All patients received ≥ 70% of the scheduled hyperthermia applications. In summary, 2/19 (11%) fulfilled the dose-limiting-toxicity (DLT) criteria, which corresponded with a feasibility rate of 90%.

Stage 2 Feasibility Analysis

Per protocol, 59 patients had to be recruited for the second stage. Because of six dropouts (see Figure 1) 59 of 65 patients enrolled qualified for this analysis; 47/59 (80%) with a LARC and 12/59 (20%) with a LRRC. No grade 4–5 adverse events occurred. No leukopenia or neutropenia of severity grade 3 with complications as mentioned above was found. Fourteen of 59 patients (24%) experienced a non-hematological toxicity of grade 3. In 5/59 patients (9%), toxicity led to permanent discontinuation of at least one of the drugs or other treatment modalities or a delay of treatment of more than three weeks. A total of 55/59 (93%) patients received ≥ 70% of the scheduled hyperthermia applications. A comprehensive case-based presentation of the dose limiting toxicities may be found in Table 2. In summary, 16/59 (27%) experienced a DLT, which corresponds to a feasibility rate of 73%.

Table 2. Case-related dose-limiting toxicities (DLT).

Cases	Allergic Reaction	Proctitis	Pain	Radiodermatitis	Nausea	Others	Discontinuation Radiotherapy	Discontinuation 5-FU	Discontinuation Oxaliplatin	Discontinuation Hyperthermia
01010		x	x	x		x				x *
02001			x							
01014			x			x				
01019						x				x
01020			x							
01023				x						
01026							x		x	
01028		x		x						
01030		x								
01031						x				
01035						x			x	x
01034				x						
01036										x *
01037	x									
01039					x	x		x	x	
01041				x						

* Patient's request. 5-FU: 5-Fluorouracil.

No grade 4–5 early toxicities occurred. A hematotoxic event grade 3 was detected in 11/105 (11%) patients; non-hematotoxic side effects grade 3 were found in 29/105 (28%) cases. During the course of the trial, 20 serious adverse events (SAEs) were recorded and recovered in 17/20 cases at the time of analysis. A comprehensive overview of early toxicity is given in Table 4.

Table 4. Adverse events according to NCI CTCAE v.4.0.

Adverse Event	Grade 1–2 n/N (%)	Grade 3 n/N (%)	N.a. n/N (%)
Anemia	71/105 (68)	1/105 (1)	6/105 (6)
Leucopenia	44/105 (42)	1/105 (1)	6/105 (6)
Neutropenia	6/105 (6)	-	6/105 (6)
Neutropenic fever	-	1/105 (1)	6/105 (6)
Thrombocytopenia	38/105 (36)	-	6/105 (6)
Elevated creatinine	15/105 (14)	-	6/105 (6)
Elevated bilirubine	12/105 (11)	-	6/105 (6)
Elevated transaminases (AST/ALT)	41/105 (39)	2/105 (2)	6/105 (6)
Elevated alkaline phosphatase	19/105 (18)	-	6/105 (6)
Aconuresis	4/105 (4)	-	7/105 (7)
Allergic reaction	11/105 (10)	2/105 (2)	7/105 (7)
Alopecia	5/105 (5)	-	7/105 (7)
Anal incontinence	29/105 (28)	1/105 (1)	7/105 (7)
Diarrhea	74/105 (70)	10/105 (10)	7/105 (7)
Dyspnea	9/105 (9)	-	7/105 (7)
Emesis	15/105 (14)	-	7/105 (7)

Erectile dysfunction	9/82 (11)	1/82 (1)	5/82 (6)
Fatigue	67/105 (64)	-	7/105 (7)
Fever	15/105 (14)	-	7/105 (7)
Hand-foot-syndrome	7/105 (7)	-	7/105 (7)
Heart disorder	5/105 (5)	-	7/105 (7)
Hemorrhage	50/105 (48)	1/105 (1)	7/105 (7)
Mucositis	18/105 (17)	1/105 (1)	7/105 (7)
Nausea	39/105 (37)	2/105 (2)	7/105 (7)
Non-infectious cystitis	53/105 (50)	2/105 (2)	7/105 (7)
Obstipation	39/105 (37)	-	7/105 (7)
Pain	56/105 (53)	4/105 (4)	7/105 (7)
Peripheral motoric neuropathy	8/105 (8)	-	7/105 (7)
Peripheral sensoric neuropathy	64/105 (61)	-	7/105 (7)
Proctitis	62/105 (59)	3/105 (3)	7/105 (7)
Radiodermatitis	71/105 (68)	7/105 (7)	7/105 (7)
Urge to urinate	40/105 (38)	-	7/105 (7)
Vaginal stenosis	3/23 (13)	-	-
Weight loss	23/105 (22)	-	7/105 (7)
Other non-hematological AEs	20/105 (19)	7/105 (7)	6/105 (6)

N.a.: not available. AEs: adverse events. AST: glutamyl oxaloacetic transaminase/aspartate aminotransferase; ALT: glutamyl pyruvic transaminase/alanine aminotransferase.

19 Statistical methods

Feasibility (2012)

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 dose limiting toxicity (DLT) 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.

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.

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. 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 (a rate of >46/59 patients fulfilling the feasibility criterion is formally deemed as a trial success), 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 is provided by confidence intervals (not corrected for the interim analysis of the SIMON design) 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%

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.

Statistical methods

All parameters (except for the formal assessment of the primary endpoint) 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), 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 (not corrected for the interim analysis in case of the primary endpoint). Additional detail analyses will be described in a statistical analysis plan to be written before embarking on the final analysis.

Interim and final analyses

As described and justified an interim analysis is performed, when 19 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.

pCR-rate (Amendment 2016)

General design and purpose of the amendment

The present trial was originally designed to show feasibility of the experimental regimen including hyperthermia. Having received a positive signal in this respect, exploring the antineoplastic treatment effect is the next logical step in the combined modality therapy development. As the resources for this treatment approach are rather limited, it seems to be inappropriate from a scientific and also ethical point of view, not to include the available evidence from the patients already included in the HyRec trial. Therefore, an extension of the HyRec trial directing to efficacy assessment is performed.

The pathologic complete response (pCR) rate, (i.e. the proportion of patients with pCR among all enrolled patients), is chosen as new primary efficacy endpoint, as this is considered to be an appropriate surrogate efficacy endpoint for the phase II part of the development of this treatment approach.

Sample size calculation

The objective of this extended trial is to find evidence that the combination with hyperthermia has superior activity compared to that of chemoradiotherapy alone, based on the existing historical evidence. Pathological complete responses are a rather rare event after standard radiochemotherapy alone in this type of patients, with and overall incidence of mostly below 10%. The few existing comparative results show pCR rates of 2% vs. 16% without or with hyperthermia, respectively, in a Russian trial dating from 1990 [29], and 7% vs. 23% in a more recent series from Tübingen [32]; in a Dutch trial the difference between the treatment arms of about 6% in the rectal cancer subgroup was considerably lower, but based on a relatively small sample [36]. In summary, a doubling of the pCR rate seems to be an achievable and clinically relevant goal.

The statistical calculation is based on the following premises and assumptions:

The experimental therapy arm would be rated as insufficiently active, if the true pCR rate is 10% or lower, as this corresponds to an equal or only irrelevantly improved efficacy compared to radiochemotherapy alone, as described above.

On the other hand, the experimental therapy would be considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true pCR rate amounted to 20% or more.

Probability to accept the experimental therapy as promising (> 20% pCR rate) with respect to efficacy, in spite of a true pCR rate of $\leq$ 10%: 0.05 (type I error, one-sided)

Probability to reject the experimental therapy as not sufficiently efficient ($\leq$ 10%), although the true pCR rate is promising (> 20%): 0.1 (type II error, corresponding to a power of 90%).

According to these parameters, and using a standard single-stage phase II design by Fleming [37], n = 102 patients evaluable for efficacy have to be recruited. In order to allow for some dropouts and to achieve a similar power in the per protocol analysis (cf. section 7.3), 110 patients are planned to be enrolled.

The final conclusion of the phase II trial will depend on the definite pCR rate (and its confidence interval), as well as other relevant information, such as on type, frequency and severity of toxicities.

Evaluation categories of patients

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

Sensitivity analyses of efficacy endpoints will be performed on the per protocol analysis set defined as the subset of the ITT analysis set, who have received the full protocol combination therapy (or experience unequivocally documented earlier progression according to RECIST) and who have no major protocol deviations thought to impact on the efficacy conclusions of the trial.

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

Statistical methods

All parameters will be evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. Corresponding to the sample size design, a two-sided 90% confidence interval will be provided for the pCR rate. If any p values are calculated (e.g. in subgroup comparisons), they are considered to be descriptive and will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. Thus, the p values will reflect the comparison-wise error and not the experiment-wise error. All p values will be two-sided if not stated otherwise. The statistical methods described in this section are suited for the data and distributions usually expected in this type of trials. The suitability will be checked after data entry. If necessary, the statistical method will be modified accordingly, with critical discussion of the original and modified results.

pCR rate (primary endpoint), toxicity, and event rates at 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 disease-free or overall survival will be estimated by the product limit method [38] and eventually compared using the logrank test. If the PETO logrank test [39, 40] is not appropriate because of violation of the proportional hazard assumption [41], Gehan's generalization [42] of the Wilcoxon rank sum test for censored data may be applied, preferably in its modification by PETO [39] and PRENTICE [43].

Multivariate analyses will eventually be performed by suitable regression models (logistic regression, proportional hazard regression model [44]).

Additional details of analysis will be described in a statistical analysis plan to be written before embarking on the final analysis.

Interim and final analyses

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

	The main biostatistical 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.
20	**Summary – Conclusions**
	The aim of this trial was to prospectively analyze feasibility (safety) and pathological complete response (pCR) rates (efficacy) of neoadjuvant chemoradiotherapy combined with regional hyperthermia in patients with locally advanced (LARC) or recurrent (LRRC) rectal cancer. Between 2012 and 2018, 111 patients with UICC stage IIB-IV or any locally recurrent rectal cancer were included. Patients received radiotherapy with concurrent 5-Fluororuracil (alternatively Capecitabine was allowed) and Oxaliplatin, and deep regional hyperthermia. Safety: Stage 1 feasibility analysis evaluated dose-limiting toxicities (DLT) after 19 patients, stage 2 after 59 evaluable patients. The feasibility rates for stages 1 and 2 were 90% (17/19) and 73% (43/59), respectively. Efficacy: Analysis of the pCR rate was based on histopathological reports. In the intention-to-treat population the pCR rate was 19% (20/105; 90% confidence interval (CI) 13.0–26.5). In the per-protocol-analysis, complete tumor regression was seen in 28% (18/64) and 38% (3/8) of the patients with LARC and LRRC, respectively. Complete resection rates (R0) among patients with LARC and LRRC who received surgery were 99% (78/84) and 67% (8/12). Conclusions: The intensified neoadjuvant and multimodality treatment schedule was feasible and led to comparable early toxicity rates as described by other trials that used the similar chemoradiation protocol. The presented treatment regimen resulted in a very high pCR rate and appears as a promising option, especially for patients with LRRC.
21	**Date of report**
	14.10.2024

Erlangen, 14.10.2024

Date

Prof. Dr. med. Oliver Ott