VOLUME 25 · NUMBER 1 · JANUARY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Phase II Trial of Chemoradiation With Oxaliplatin for Rectal Cancer

Claus Rödel, Torsten Liersch, Robert Michael Hermann, Dirk Arnold, Thomas Reese, Matthias Hipp, Alois Fürst, Nimrod Schwella, Michael Bieker, Gunter Hellmich, Hermann Ewald, Jörg Haier, Florian Lordick, Michael Flentje, Heiko Sülberg, Werner Hohenberger, and Rolf Sauer

From the Departments of Radiation Therapy and Surgery, University of Erlangen-Nürnberg, Erlangen; Departments of General Surgery and Radiation Oncology and Radiotherapy, University of Göttingen, Göttingen; Departments of Haematology and Oncology and Radiotherapy, Martin Luther University Halle-Wittenberg, Halle-Wittenberg; Department of Radiotherapy, University of Regensburg; Department of Surgery, Caritas-Hospital St Josef, Regensburg; Departments of Haematology, Oncology, and Immunology and Radiotherapy, Philipps-University Hospital, Marburg; Department of General and Abdominal Surgery, Dresden-Friedrichstadt Hospital, and Teaching Hospital of Technical University Dresden, Dresden; Department of General Surgery and Thoracic Surgery, University Hospital of Schleswig-Holstein, Kiel; Department of General Surgery, University Hospital Münster, Münster; Third Department of Internal Medicine (Hematology/Medical Oncology), Klinikum Rechts der Isar, Technical University of Munich, Munich; Department of Radiation Oncology, University of Würzburg, Würzburg; and WiSP Research Institute, Langenfeld, Germany.

Submitted July 25, 2006; accepted October 5, 2006.

Supported by a grant from Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany, and Sanofi-Aventis Pharma GmbH, Berlin, Germany.

Presented in part at the 2006 Gastrointestinal Cancers Symposium, January 26-28, 2006, San Francisco, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Claus Rödel, MD, Department of Radiotherapy, University of Erlangen, Universitätsstr 27, 91054 Erlangen, Germany; e-mail: claus.roedel@strahlen.med.uni-erlangen.de.

0732-183X/07/2501-110/$20.00

DOI: 10.1200/JCO.2006.08.3675

ABSTRACT

Purpose
To evaluate the activity and safety of preoperative radiotherapy (RT) and concurrent capecitabine and oxaliplatin (XELOX-RT) plus four cycles of adjuvant XELOX in patients with rectal cancer.

Patients and Methods
One hundred ten patients with T3/T4 or N+ rectal cancer were entered onto the trial in 11 investigator sites and received preoperative RT (50.4 Gy in 28 fractions). Capecitabine was administered concurrently at 1,650 mg/m^2 on days 1 to 14 and 22 to 35, and oxaliplatin was administered at 50 mg/m^2 on days 1, 8, 22, and 29. Surgery was scheduled 4 to 6 weeks after completion of XELOX-RT. Four cycles of adjuvant XELOX (capecitabine 1,000 mg/m^2 bid on days 1 to 14; oxaliplatin 130 mg/m^2 on day 1) were administered. The main end points were activity as assessed by the pathologic complete response (pCR) rate and the feasibility of postoperative XELOX chemotherapy.

Results
After XELOX-RT, 103 of 104 eligible patients underwent surgery; pCR was achieved in 17 patients (16%), one patient had ypT0N1 disease, and 53 patients showed tumor regression of more than 50% of the tumor mass. R0 resections were achieved in 95% of patients, and sphincter preservation was accomplished in 77%. Full-dose preoperative XELOX-RT was administered in 96%. Grade 3 or 4 diarrhea occurred in 12% of patients. Postoperative complication occurred in 43% of patients. Sixty percent of patients received all four cycles of adjuvant XELOX, with sensory neuropathy (18%) and diarrhea (12%) being the main grade 3 or 4 toxicities.

Conclusion
Preoperative XELOX-RT plus four cycles of adjuvant XELOX is an active and feasible treatment. This regimen is proposed for phase III evaluation comparing standard fluorouracil-based treatment with XELOX- based multimodality treatment.

J Clin Oncol 25:110-117. © 2007 by American Society of Clinical Oncology

INTRODUCTION

Fluorouracil (FU) -based chemoradiotherapy (CRT) improved survival for locally advanced rectal cancer when used in the postoperative setting.[1,2] A phase III trial of our group demonstrated that preoperative FU CRT plus four cycles of postoperative FU chemotherapy is superior to standard postoperative treatment in terms of local control and acute and long-term toxicity.[3] Two recent phase III trials from the European Organisation for Research and Treatment of Cancer (EORTC), EORTC 22921, and the Fédération Francophone de Cancérologie Digestive (FFCD), FFCD 9293, have confirmed the advantages of preoperative FU CRT over radiotherapy (RT) alone with respect to local control rates, but in none of these phase III trials was survival significantly improved.[4,5] Thus, with optimized local treatment, including preoperative FU CRT and total mesorectal excision, local relapse rates have now been reduced to 5% to 10%; however, distant metastases still occur in 25% to 30% of patients. Evidently, any further improvement will require the integration of more effective systemic therapy into the multimodality concept.

Although attempts to improve the efficacy of FU-based CRT by incorporation of semustine or FU modulation through folinic acid or levamisole have failed to demonstrate any significant benefit, continuous infusion of FU during RT has been shown to be superior to bolus FU regarding disease-free and overall survival.[6-8] Capecitabine is an oral fluoropyrimidine that imitates the pharmacokinetics of continuous FU infusion and is preferentially converted

to the active metabolite within tumor cells by exploiting the higher activity of the enzyme thymidine phosphorylase in tumor tissue compared with normal tissue.[9] This tumor-selective activation of capecitabine is improved further when combined with RT, which upregulates thymidine phosphorylase in tumor cells but not in healthy tissue.[10] Oxaliplatin, one of the most active single agents in the treatment of colorectal cancer, is also a reasonable candidate for combined-modality programs because of its relative lack of acute dose-limiting adverse effects when added to RT and FU/capecitabine. Recent preclinical studies have demonstrated oxaliplatin to be a potent radiosensitizing agent.[11,12] Moreover, results from two recent studies have shown that the addition of oxaliplatin to FU/leucovorin improves disease-free survival of patients with stage II and III colon cancer.[13,14]

The aim of this multicenter phase II trial was to confirm the activity and safety of our recently published single-center neoadjuvant capecitabine and oxaliplatin (XELOX) -RT protocol in a multi-institutional setting with 110 patients included at 11 investigator sites.[15] Moreover, because the cumulative doses of these drugs applied during preoperative CRT are substantially lower than in adjuvant colon cancer trials, the safety and feasibility of four additional adjuvant cycles of XELOX were tested. The overall aim was to establish a regimen of preoperative XELOX-RT followed by surgery plus adjuvant chemotherapy with XELOX that could be proposed for phase III evaluation versus standard FU CRT plus adjuvant FU.

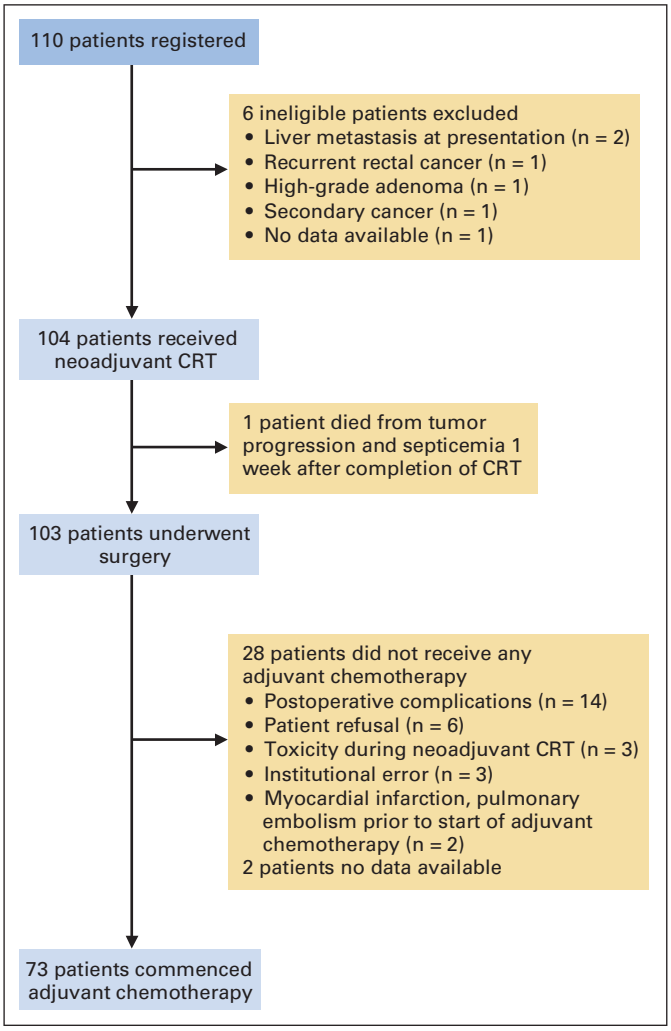

Fig 1. Trial progress. CRT, chemoradiotherapy.

Table 1. Baseline Characteristics

Characteristic	No. of Patients (N = 104)	%
Age, years		
Median	61	
Range	39-77	
Sex		
Male	73	70
Female	31	30
ECOG performance status		
0	85	82
1	18	17
2	1	1
TN clinical staging		
T2N1-2	3	3
T3N0/X	23	22
T3N1-2	63	61
T4N0/X	2	2
T4N1-2	13	12
Distance of lower tumor margin to anal verge, cm		
Mean	6.3	
SD	3.3	
Range	0-16	
Lower third, ≤ 6 cm	53	51
Middle third, 6-12 cm	45	43
Upper third, ≥ 12 cm	3	3
Unknown	3	3

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TN, tumor-node; SD, standard deviation.

PATIENTS AND METHODS

This study was approved by the ethics committee of the University of Erlangen (Nr. 3085) and by all local review boards of the participating institutions. Each patient gave written informed consent before being accrued.

Eligibility Criteria

Eligibility criteria included histopathologically confirmed rectal adenocarcinoma with the inferior margin within 16 cm from anal verge as assessed by rigid rectoscopy. The tumor had to have evidence of T3 or T4 disease and/or positive perirectal lymph nodes by endorectal ultrasound, multisclice computed tomography (CT), or magnetic resonance imaging of the pelvis. Further inclusion criteria were Eastern Cooperative Oncology Group performance status ≤ 2 and adequate hematologic, liver, and renal function (neutrophils $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, creatinine clearance > 50 mL/min, total bilirubin concentration < 2× the upper normal limit, and liver transaminase or alkaline phosphatase concentrations < 3× the upper normal limit). Patients were excluded for metastatic disease, prior RT to the pelvic region or previous chemotherapy, and other cancers. Patients suffering from the following conditions were also ineligible: inflammatory bowel disease, malabsorption syndrome, previous history of cardiac arrhythmia or coronary heart disease, peripheral neuropathy, and psychiatric disorders or psychological disabilities thought to adversely affect treatment compliance. Pregnant or lactating patients and women with childbearing potential who lacked effective contraception were excluded. No upper age limit was defined.

Pretreatment Evaluation

Pretreatment evaluation included a complete history and physical examination, biopsy, digital rectal examination, rigid rectoscopy, colonoscopy,

Table 2. Pathologic Staging (n = 103)*

Baseline Staging	Total No. of Patients	No. of Patients							
		ypT0	ypT1	ypT2	ypT3	ypT4	ypN0†	ypN1†	ypN2†
T2	3	1	1		1				
T3	86	14	5	35	31	1			
T4	14	3	1	3	6	1			
Node negative/x	25						23	1	1
Node positive	78						53	17	8
Total	103	18‡	7	38	38	2	76	18	9

*Tumor downstaging occurred in 69 (67%) of 103 patients; nodal downstaging occurred in 53 (68%) of 78 patients.
†The median numbers of lymph nodes investigated for ypN0, ypN1, and ypN2 were 12 (range, two to 47 nodes), 14 (range, two to 31 nodes), and 15 (range, nine to 28 nodes).
‡ypT0N0: 17 patients; ypT0N1: one patient.

endorectal ultrasound, CT or magnetic resonance imaging of the pelvis, abdominal CT, and chest x-ray. Complete laboratory tests included a full blood count, blood electrolytes, creatinine, urea, liver transaminases, alkaline phosphatase, and total bilirubin. Cardiac function was investigated both by an ECG and an echocardiogram.

Treatment

Neoadjuvant CRT (XELOX-RT). RT was delivered with x-ray by a linear accelerator with minimum of 6 MV through a three- or four-field box technique to the primary tumor and mesorectal, presacral, and internal iliac lymph nodes up to the level of the bottom of the fifth lumbar vertebra. Irradiation techniques and treatment volumes have been described in detail elsewhere.[15] All patients received a total dose of 50.4 Gy, with daily fractions of 1.8 Gy on 5 days per week. During preoperative treatment, capecitabine was delivered orally at a fixed dose of 825 mg/m^2 twice daily on days 1 to 14 and 22 to 35 of RT. The first daily dose was administered approximately 2 hours before RT, with the second dose administered 12 hours later. Oxaliplatin was administered as a 2-hour infusion on days 1, 8, 22, and 29 at a dose of 50 mg/m^2/d, as previously established in our single-center phase I/II study.[15]

Patients were monitored weekly regarding history, clinical examination, blood count, and biochemistry including liver function. We did not modify the RT schedule for grade $\leq$ 2 toxicities unless the severity worsened. The doses of capecitabine and oxaliplatin were adjusted for adverse events according to a standard scheme, which is described in detail by Rödel et al.[15]

Adjuvant chemotherapy (XELOX). Four to 6 weeks after surgery, patients received another 12 weeks of capecitabine at a dose of 2,000 mg/m^2/d for 14 days, every 21 days. Oxaliplatin was administered on day 1 of each of four cycles at a dose of 130 mg/m^2/d. The indication to apply postoperative chemotherapy was based on pretreatment staging results (ie, patients with downstaging to International Union Against Cancer [UICC] stage 0 or I after preoperative CRT were also eligible for postoperative chemotherapy). The following recommendations for chemotherapy dose reductions were applied: in case of grade $\geq$ 2 toxicity according to National Cancer Institute Common Toxicity Criteria,[16] capecitabine was interrupted, and appropriate symptomatic treatment was administered. When the toxicity resolved to grade 0 or 1, treatment was continued at 75% of the original dose in case of the first appearance of the respective toxicity and at 50% of the starting dose in case of the second appearance. The dose of oxaliplatin was reduced for grade 3 vomiting, grade 3 or 4 thrombocytopenia or neutropenia, and for paresthesia with pain or functional impairment of more than 7 days in duration. For paresthesia with functional impairment persistent between cycles, oxaliplatin was discontinued.

Surgery and Pathology

Four to 6 weeks after completion of XELOX-RT, total mesorectal excision was performed according to a standardized technique. Assessment of the intended surgical procedure (ie, whether sphincter preservation was deemed possible or not) was performed by the treating surgeon

Table 3. Surgical Parameters and TRG of the Primary Tumor After Neoadjuvant Chemoradiotherapy

Parameter	No. of Patients (n = 103)	%
Type of surgery		
Anterior/low anterior resection	69	67
Intersphincter resection	9	9
Defunctioning stoma, n = 78	59	76
APR	24	23
Harmann's operation	1	1
Resection		
Adjacent organs	18*	17
Metastases	3†	3
Sphincter preservation in subgroup of patients judged by the surgeon to need APR, n = 29	12	41
Resection status		
R0	98	95
R1	1	1
R2	2	2
Rx	2	2
TRG, n = 96‡		
TRG 4, complete regression	18	19
TRG 3, > 50% of tumor mass	53	55
TRG 2, $\geq$ 25%-50% of tumor mass	11	11
TRG 1, < 25% of tumor mass	11	11
TRG 0, no regression	3	3
Surgical complications	44	43
Wound healing	19	18
Anastomotic leak§	12	12
Urinary retention	9	9
Ileus	3	3
Fistula	6‖	6
Bleeding	2	2
Infection	5	5
Cardiovascular	2	2
Reoperation necessary	7¶	7

Abbreviations: TRG, tumor regression grade; APR, abdominoperineal resection.
*Prostate/seminal: n = 8; vagina/uterus: n = 4; bladder: n = 3; other: n = 3.
†Wedge resection of liver metastases: n = 2; peritoneal: n = 1.
‡Percentages refer to patients reported for TRG (n = 96).
§Defined as extravasation of water-soluble contrast on radiologic examination and/or clinically symptomatic leakage (peritonitis or pelvic abscess).
‖Fistula to urinary bladder: n = 3, vagina: n = 3.
¶Wound healing: n = 3; bleeding: n = 2; ileus: n = 1; fistula: n = 1.

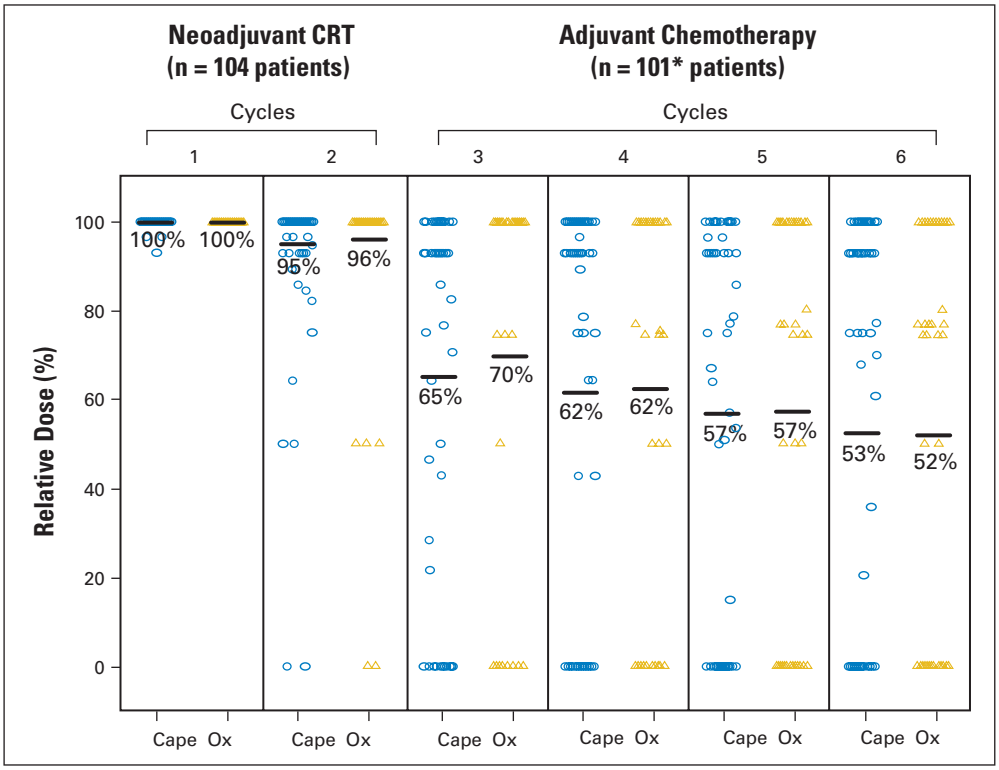

Fig 2. Mean relative dose-intensities of capecitabine (Cape) and oxaliplatin (Ox) during neoadjuvant chemoradiotherapy (CRT) and four cycles of adjuvant chemotherapy. The circles (Cape) and triangles (Ox) plot the dose-intensity relative to the prescribed dose for every individual patient. The bars represent the mean relative dose-intensity for all patients. (*) One patient died before surgery, and two patients with no information after surgery were excluded; 28 patients not receiving adjuvant chemotherapy (see Fig 1) were plotted at 0%.

before start of treatment. If adjacent organs were involved intraoperatively, surgery was extended to partial or total resection of adjacent pelvic organs.

The extent of residual tumor in the resected specimen was classified according to the TNM staging system of the American Joint Committee on Cancer (AJCC)/UICC, using the prescript "y" to indicate that the tumor has been treated before surgical resection.[17] Residual tumor mass, fibrotic changes, and irradiation vasculopathy after preoperative XELOX-RT were semiquantitatively evaluated according to a 5-point rectal cancer regression grading established by Dworak et al[18] and evaluated for its prognostic impact by our group previously.[19] A pathologic complete response (pCR) was defined as the absence of viable tumor cells in the primary tumor and in the lymph nodes (ypT0N0).

Study Design

The primary end point of this phase II study was the pCR rate after neoadjuvant XELOX-RT. Current standard preoperative FU CRT yields pCR rates in the range of 5% to 10%.[3-5] Using a single-stage design according to Fleming,[20] a pCR rate of 15% was considered to qualify the experimental treatment for further testing. A pCR rate of $\leq 7.5\%$ was ruled out as futile. With a sample size of 96 patients, the risk of erroneously claiming sufficient activity despite a true pCR rate of $\leq 7.5\%$ (type I error) amounted to 5%, with a type II error probability of mistakenly rejecting XELOX-RT in case of truly promising activity set to 20%, corresponding to a power of 80%. The planned patient number was increased to 110 to allow for drop-outs. Secondary end points included toxicity and compliance with the regimen, R0 resection rates, rates of sphincter-sparing surgery, tumor regression grades, pathologic downstaging, and 1-month surgical complications.

RESULTS

A total of 110 patients were enrolled between April 2004 and March 2005. Figure 1 shows the progress of all patients during the trial. Six patients were ineligible; Table 1 lists the baseline characteristics of the remaining 104 patients.

Efficacy and Surgical Parameters

After neoadjuvant CRT, 103 patients underwent surgery. pCR (ypT0N0M0) was achieved in 17 patients (16% as calculated for the intent-to-treat population of 104 patients); one patient had ypT0N1 disease (Table 2). Comparing the diagnostic work-up stage with the pathologic stage, tumor downstaging with respect to the tumor stage was observed in 69 (67%) of 103 patients, and downstaging with respect to the nodal stage was observed in 53 (68%) of 78 patients (Table 2). Complete tumor regression of the primary tumor (ypT0, tumor regression grade 4) was achieved in 18 patients, and an additional 53 patients showed tumor regression of more than 50% of the tumor mass (tumor regression grade 3; Table 3).

R0 resections were achieved in 98 patients (95%; Table 3). Sphincter-sparing surgery was performed in 79 (77%) of all 104 patients and in 12 (41%) of 29 patients judged by the surgeon to require abdominoperineal resection before CRT. For low-lying tumors less than 6 cm from the anal verge, the sphincter preservation rate was 63%.

Compliance With the Regimen and Toxicity

Neoadjuvant CRT. RT was applied as prescribed in 95 (91%) of 104 patients. Unplanned treatment interruptions of more than 2 days as a result of toxicity occurred in five patients (5%; all completed full-dose RT). In four patients (4%), RT was discontinued as a result of diarrhea (n = 2), ileus (n = 1), and genitourinary toxicity (n = 1) after 19.8, 34.2, and 41.4 Gy (2×), respectively. The mean relative dose-intensity of both capecitabine and oxaliplatin during neoadjuvant

CRT was 100% and 95% to 96% for the first and second cycles, respectively (Fig 2).

Surgery. Total mesorectal excision surgery was performed after a median interval of 6.1 weeks (range, 4.9 to 9.3 weeks) from completion of XELOX-RT. One-month postsurgical complications of any grade were noted in 44 patients (43%; Table 3). These occurred mainly as wound healing problems (18%) and anastomotic leakage (12%). Seven patients (7%) required a reoperation; no patient died from postoperative complications.

Adjuvant chemotherapy. Of the 103 resected patients, 73 (71%) commenced adjuvant chemotherapy after a median interval of 5.3 weeks (range, 3.1 to 19.1 weeks), and 28 patients (27%) did not receive any postoperative chemotherapy, mainly because of postoperative complications (n = 14, 50%) or patient refusal (n = 6, 21%; Fig 1). A total of 61 patients (60%) received all four adjuvant chemotherapy cycles. The protocol-specified duration of four cycles (14 days of treatment, 7 days of rest) was 84 days; the median and mean (± standard deviation) duration for the 61 patients who completed all four cycles was 84 days and 86 days (± 7.5 days), respectively. Sixty-five patients (64%) received at least three cycles, and 68 patients (67%) received at least two cycles (with or without dose reduction). With appropriate dose reduction as a result of treatment-induced toxicity and including the 28 patients with complete omission of adjuvant chemotherapy, the mean relative dose-intensity of capecitabine and oxaliplatin, as calculated for the entire cohort of 101 patients (two patients with no information were excluded), decreased to 53% and 52% in the last cycle, respectively (Fig 2). If expressed by the number of patients who received at least 75% of the prescribed cumulative doses of chemotherapy, the relative dose-intensities were 50% (51 of 101 patients) for capecitabine and 53% (54 of 101 patients) for oxaliplatin.

Toxicity. Table 4 lists the incidence of acute toxicity during neoadjuvant CRT and adjuvant chemotherapy. Two deaths occurred; one death occurred shortly after completion of preoperative CRT as a result of septicemia and tumor progression in a female patient with a large tumor extending to the bladder and uterus, and the other death occurred in a male patient who died from cardiac arrest after the first adjuvant chemotherapy cycle with no prior signs or symptoms of cardiac toxicity. Diarrhea was the most common severe toxicity during neoadjuvant CRT, with 12 patients (12%) suffering from grade 3 or 4 diarrhea. In the adjuvant setting, grade

Table 4. Treatment-Induced Toxicity

	Neoadjuvant Chemoradiotherapy (n = 104)						Adjuvant Chemotherapy (n = 73)					
	Grade 1/2		Grade 3		Grade 4		Grade 1/2		Grade 3		Grade 4	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Blood/bone marrow												
Leukopenia	52	50	3	3	1	1	47	64	1	1	—	—
Thrombocytopenia	23	22	—	—	—	—	30	41	2	3	—	—
Anemia	54	52	1	1	—	—	55	75	—	—	—	—
Gastrointestinal												
Diarrhea	57	55	11	11	1	1	24	33	8	11	1	1
Nausea/vomiting	50	48	5	5	1	1	49	67	5	7	1	1
Stomatitis	7	7	1	1	—	—	5	7	—	—	—	—
Obstipation/ileus	8	8	1	1	1	1	3	4	—	—	—	—
Proctitis	10	10	—	—	—	—	—	—	—	—	—	—
Renal/genitourinary												
Dysuria	30	29	3	3	—	—	6	8	1	1	—	—
Creatinine	16	15	1	1	—	—	12	16	1	1	—	—
Proteinuria	12	12	—	—	—	—	12	16	—	—	—	—
Sensory neuropathy	36	35	—	—	—	—	39	53	13	18	—	—
Dermatology/skin												
Hand-foot syndrome	8	8	1	1	—	—	25	34	1	1	—	—
Radiation dermatitis	47	45	1	1	—	—	2	3	—	—	—	—
Cardiac toxicity	3	3	1	1	—	—	2	3	3	4	1*	1
Metabolic/laboratory												
Hyperbilirubinemia	16	15	—	—	—	—	17	23	—	—	—	—
Transaminases, AST, ALT	36	35	4	4	—	—	36	49	1	1	—	—
Alkaline phosphatase	17	16	—	—	—	—	28	38	—	—	—	—
Hypocalcemia/hypokalemia	—	—	—	—	—	—	9	12	—	—	—	—
Allergy/immunology												
Allergic reaction/hypersensitivity	17	16	—	—	1	1	13	18	1	1	—	—
Interleukin-releasing syndrome	9	9	—	—	—	—	4	5	—	—	—	—
Infection	3	3	5	5	1†	1	5	7	1	1	1	1

*Grade 5; death from cardiac arrest after the first cycle.
†Grade 5; death from septicemia and tumor progression.

3 sensory neuropathy (18%) and diarrhea (12%) were the predominant grade 3 or 4 toxicities.

DISCUSSION

The preoperative part of this multi-institutional phase II trial confirmed the findings of our single-center phase I and II preoperative XELOX-RT trial.[15] For both studies, the same inclusion criteria and preoperative CRT regimen were applied. pCR rates were 19% and 16%; compliance rates were 89% and 96%; grade 3 or 4 diarrhea, which was the most common toxicity during neoadjuvant treatment, was restricted to 8% and 12%; and postoperative complications of any grade occurred in 39% and 43% of patients in the single-center and multicenter XELOX-RT studies, respectively. The respective figures for preoperative CRT in our previous phase III trial (using the same inclusion criteria and RT schedule, but using FU instead of XELOX) were 8% for pCR rate, 89% for overall treatment compliance, 12% for grade 3 or 4 diarrhea, and 36% for postoperative complications of any grade.[3] Despite the limitations of cross-study comparisons, this preoperative XELOX-RT regimen seems to be more active in terms of local tumor regression (pCR) compared with our standard FU CRT protocol.

The following three different schedules for incorporating XELOX into preoperative CRT have been published so far (Table 5): (1) synchronous oxaliplatin, capecitabine, RT, and elective surgery (SOCRATES)[21,22]; (2) RT, oxaliplatin, and capecitabine (RadiOxCape)[23] and capecitabine, oxaliplatin, RT, and excision (CORE)[24]; and (3) our XELOX-RT regimen. The cumulative doses of capecitabine, oxaliplatin, and RT with these three different regimens were as follows: (1) 42,900 mg/m^2, 260 mg/m^2, and 45 Gy; (2) 41,250 mg/m^2, 250 mg/m^2, and 45 Gy, and (3) 46,200 mg/m^2, 200 mg/m^2, and 50.4 Gy, respectively. All three XELOX-RT schedules seem to be equally active and tolerable and may now be tested in larger phase III trials.

Although many different preoperative CRT schedules with incorporation of new drugs and combinations, including oxaliplatin, irinotecan, cetuximab, and bevacizumab, have been published in recent years, there are, to our knowledge, only two phase II trials worldwide, the CORE study and our trial, to test the feasibility and tolerability of incorporating combination therapies both into preoperative CRT and adjuvant chemotherapy for rectal cancer patients. Given that, in colon cancer adjuvant trials, the cumulative doses of, for example, oxaliplatin were 1,020 mg/m^2 over 24 weeks in the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer trial and 765 mg/m^2 over 24 weeks in the National Surgical Adjuvant Breast and Bowel Project protocol C-07 trial, it is unlikely that the cumulative doses of oxaliplatin that can be safely applied during preoperative CRT (200 to 260 mg/m^2 over 5 to 6 weeks) exert adequate systemic efficacy.[13,14] Thus, we designed this phase II trial to establish a regimen of preoperative XELOX-RT plus adjuvant XELOX that could subsequently be compared with standard preoperative FU CRT and four cycles of adjuvant FU (ie, the best arm of our former phase III trial).[3]

The most important results of this second part of our study are that 60% of the entire cohort of 103 operated patients completed all four XELOX cycles (with or without dose reduction), that 50% and 53% of patients received at least 75% of the prescribed doses of capecitabine and oxaliplatin, respectively, and that 27% of patients, for different reasons, did not receive any adjuvant chemotherapy. The CORE study reported similar figures with 30 (35%) of 85 patients not receiving any adjuvant XELOX and with a further 12 (14%) of 85 patients who stopped adjuvant chemotherapy prematurely.[24] It is evident that preoperative CRT, surgical complications, and the fact that a substantial part of patients will have pCR or yUICC stage I and II tumors as a result of downstaging effects or initial clinical staging error compromise the possibility and willingness of patients to tolerate postoperative chemotherapy. However, this is true not only for patients treated with more active protocols, such as XELOX-RT, but also for patients treated with standard FU CRT. In three recent, large, phase III trials of preoperative FU CRT plus postoperative FU chemotherapy (EORTC 22921,

Table 5. Trials With XELOX-Based Neoadjuvant Chemoradiotherapy With or Without Adjuvant Chemotherapy for Rectal Cancer

Series	No. of Patients	Neoadjuvant XELOX-RT	Adjuvant Chemotherapy	Grade 3/4 Toxicity*	pCR (%)
SOCRATES; Glynne-Jonesr et al[20,21]	85	RT 1.8-45 Gy; capecitabine 650 mg/m^2 bid, 7 d/wk; oxaliplatin 130 mg/m^2 on days 1 and 29	None	Diarrhea: 9%	19
RadiOxCape; Machiels et al[23]	40	RT 1.8-45 Gy; capecitabine 825 mg/m^2 bid, 5 d/wk; oxaliplatin 50 mg/m^2 once weekly	FU/LV recommended for ypN+	Diarrhea: 30%	14
CORE; Rutten et al[24]	87	RT 1.8-45 Gy; capecitabine 825 mg/m^2 bid, 5 d/wk; oxaliplatin 50 mg/m^2 once weekly	6 cycles (14 days of treatment, 7 days of rest): capecitabine 1 g/m^2 bid, days 1 to 14; oxaliplatin 130 mg/m^2 on day 1	Diarrhea: 18%	10
XELOX-RT; present study	104	RT 1.8-50.4 Gy; capecitabine 825 mg/m^2 bid, days 1-14 + 22-35; oxaliplatin 50 mg/m^2/d, days 1, 8, 22, and 29	4 cycles (14 days of treatment, 7 days of rest): capecitabine 1 g/m^2 bid, days 1-14; oxaliplatin 130 mg/m^2 on day 1	Diarrhea: 12%	16

Abbreviations: XELOX, capecitabine and oxaliplatin; RT, radiotherapy; pCR, pathologic complete response; SOCRATES, Synchronous Oxaliplatin, Capecitabine, Radiotherapy and Elective Surgery; RadiOxCape, Radiotherapy, Oxaliplatin, and Capecitabine; FU, fluorouracil; LV, leucovorin; CORE, Capecitabine, Oxaliplatin, Radiotherapy and Excision.
*Refers to neoadjuvant XELOX-RT.

FFCD 9293, and our German trial), a total of 25%, 23%, and 20% of patients, respectively, did not start postoperative chemotherapy.[3-5]

Currently, there are three different approaches to address this problem in the management of rectal cancer. The first one is to completely omit postoperative chemotherapy or leave the decision to apply adjuvant chemotherapy to the individual physician or participating center, as was done in most phase II trials of preoperative CRT with new drugs, but also in phase III studies that primarily address local end points (National Surgical Adjuvant Breast and Bowel Project R-04 in the United States and Actions Concertées dans les Cancers Colorectaux et Digestifs 12/0405 in France). The second approach is to apply neoadjuvant chemotherapy before preoperative CRT rather than adjuvant chemotherapy.[25-27] This strategy avoids the problems of postoperative chemotherapy but is associated with its own caveats, such as selection of radioresistant clones, possibly reduced compliance to CRT, and substantial delay of definitive surgery.[28] The third approach is the one currently adopted by most groups (E5204 Intergroup Trial in the United States and Pan-European Trials in Adjuvant Colon Cancer 6 in Europe) that have designed phase III comparisons of standard FU versus more intense CRT protocols. These trials stick to the concept of preoperative CRT plus adjuvant chemotherapy and simply accept that a certain percentage of patients will not receive protocol-conformal postoperative chemotherapy. A fourth approach, which has not yet been tested in prospective phase III clinical studies, would be to tailor postoperative treatment according to risk factors or response parameters, such as tumor regression, circumferential resection margin invasion, and, probably most important, nodal status (ypN0 *v* ypN1/2).[19,29,30]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment: N/A **Leadership:** N/A **Consultant:** Dirk Arnold, Hoffmann-La Roche AG, Sanofi-Aventis; Florian Lordick, Hoffmann-La Roche AG, Sanofi-Aventis GmbH; Michael Flentje, Sanofi-Aventis GmbH **Stock:** N/A **Honoraria:** Claus Rödel, Hoffmann-La Roche AG, Sanofi-Aventis GmbH; Florian Lordick, Hoffmann-La Roche AG, Sanofi-Aventis GmbH **Research Funds:** Claus Rödel, Hoffmann-La Roche AG, Sanofi-Aventis GmbH; Florian Lordick, Sanofi-Aventis GmbH **Testimony:** N/A **Other:** N/A

AUTHOR CONTRIBUTIONS

Conception and design: Claus Rödel, Torsten Liersch, Dirk Arnold, Michael Flentje, Heiko Sülberg, Werner Hohenberger, Rolf Sauer
Administrative support: Claus Rödel, Gunter Hellmich
Provision of study materials or patients: Claus Rödel, Torsten Liersch, Robert Michael Hermann, Dirk Arnold, Thomas Reese, Matthias Hipp, Alois Fürst, Nimrod Schwella, Michael Bieker, Gunter Hellmich, Hermann Ewald, Jörg Haier, Florian Lordick, Michael Flentje, Werner Hohenberger, Rolf Sauer
Collection and assembly of data: Claus Rödel, Torsten Liersch, Robert Michael Hermann, Dirk Arnold, Thomas Reese, Matthias Hipp, Alois Fürst, Nimrod Schwella, Michael Bieker, Gunter Hellmich, Hermann Ewald, Jörg Haier, Florian Lordick, Michael Flentje, Heiko Sülberg, Werner Hohenberger, Rolf Sauer
Data analysis and interpretation: Claus Rödel, Torsten Liersch, Robert Michael Hermann, Dirk Arnold, Thomas Reese, Matthias Hipp, Alois Fürst, Nimrod Schwella, Michael Bieker, Gunter Hellmich, Hermann Ewald, Jörg Haier, Florian Lordick, Michael Flentje, Heiko Sülberg, Werner Hohenberger, Rolf Sauer
Manuscript writing: Claus Rödel, Torsten Liersch, Robert Michael Hermann, Dirk Arnold, Thomas Reese, Matthias Hipp, Alois Fürst, Nimrod Schwella, Michael Bieker, Gunter Hellmich, Hermann Ewald, Jörg Haier, Florian Lordick, Michael Flentje, Heiko Sülberg, Werner Hohenberger, Rolf Sauer
Final approval of manuscript: Claus Rödel, Torsten Liersch, Robert Michael Hermann, Dirk Arnold, Thomas Reese, Matthias Hipp, Alois Fürst, Nimrod Schwella, Michael Bieker, Gunter Hellmich, Hermann Ewald, Jörg Haier, Florian Lordick, Michael Flentje, Heiko Sülberg, Werner Hohenberger, Rolf Sauer

REFERENCES

1. Gastrointestinal Tumor Study Group: Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med 312:1465-1472, 1985
2. Krook JE, Moertel CG, Gunderson LL, et al: Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 324:709-715, 1991
3. Sauer R, Becker H, Hohenberger W, et al: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731-1740, 2004
4. Bosset JF, Calais G, Mineur L, et al: Preoperative radiation (Preop RT) in rectal cancer: Effect and timing of additional chemotherapy (CT) 5-year results of the EORTC 22921 trial. J Clin Oncol 23: 247s, 2005 (suppl; abstr 3505)
5. Gerard JP, Bonnetain F, Conroy T, et al: Preoperative (preop) radiotherapy (RT) + 5 FU/folinic acid (FA) in T3-4 rectal cancers: Results of the FFCD 9203 randomized trial. J Clin Oncol 23:247s, 2005 (suppl; abstr 3504)
6. Gastrointestinal Tumor Study Group: Radiation therapy and fluorouracil with or without semustine for the treatment of patients with surgical adjuvant adenocarcinoma of the rectum. J Clin Oncol 10:549-557, 1992
7. Tepper JE, O'Connell M, Niedzwiecki D, et al: Adjuvant therapy in rectal cancer: Analysis of stage, sex, and local control—Final report of intergroup 0114. J Clin Oncol 20:1744-1750, 2002
8. O'Connell MJ, Martenson JA, Wieand HS, et al: Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 331:502-507, 1994
9. Schuller J, Cassidy J, Dumont E, et al: Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 45:291-297, 2000
10. Sawada N, Ishikawa T, Sekiguchi F, et al: X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. Clin Cancer Res 5:2948-2953, 1999
11. Cividalli A, Ceciarelli F, Livdi E, et al: Radiosensitization by oxaliplatin in a mouse adenocarcinoma: Influence of treatment schedule. Int J Radiat Oncol Biol Phys 52:1092-1098, 2002
12. Magne N, Fischel JL, Formento P, et al: Oxaliplatin-5-fluorouracil and ionizing radiation: Importance of the sequence and influence of p53 status. Oncology 64:280-287, 2003
13. Andre T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343-2351, 2004
14. Wolmark N, Wienand S, Kuebler JP, et al: A phase III trial comparing FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07. J Clin Oncol 23:246s, 2005 (suppl; abstr 3500)
15. Rödel C, Grabenbauer GG, Papadopoulos T, et al: Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer. J Clin Oncol 21:3098-3104, 2003
16. Trotti A, Colevas AD, Setser A, et al: CTCAE v3.0: Development of a comprehensive grading

system for the adverse effects of cancer treatment. Semin Radiat Oncol 13:176-181, 2003

17. Greene FL, Page DL, Fleming ID, et al: Colon and Rectum, AJCC Cancer Staging Manual (ed 6). New York, NY, Springer, 2002, pp 113-124

18. Dworak O, Keilholz L, Hoffmann A: Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 12:19-23, 1997

19. Rödel C, Martus P, Papadoupolos T, et al: Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 23:8688-8696, 2005

20. Fleming TR: One-sample multiple testing procedure for phase II clinical trials. Biometrics 38:143-151, 1982

21. Glynne-Jones R, Sebag-Montefiore D, Maughan TS, et al: A phase I dose escalation study of continuous oral capecitabine in combination with oxaliplatin and pelvic radiation (XELOX-RT) in patients with locally advanced rectal cancer. Ann Oncol 17:50-56, 2006

22. Glynne-Jones R, Dunst J, Sebag-Montefiore D: The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: How successful have we been? Ann Oncol 17:361-371, 2006

23. Machiels JP, Duck L, Honhon B, et al: Phase II study of preoperative oxaliplatin, capecitabine and external beam radiotherapy in patients with rectal cancer: The RadiOxCape study. Ann Oncol 16:1898-1905, 2005

24. Rutten H, Sebag-Montefiori D, Glynne-Jones R, et al: Capecitabine, oxaliplatin, radiotherapy, and excision (CORE) in patients with MRI-defined locally advanced rectal adenocarcinoma: Results of an international multicenter phase II study. J Clin Oncol 24:153s, 2006 (suppl; abstr 3528)

25. Chau I, Brown G, Cunningham D, et al: Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol 24:668-674, 2006

26. Calvo FA, Serrano FJ, Diaz-Gonzalez JA, et al: Improved incidence of pT0 downstaged surgical specimens in locally advanced rectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and preoperative chemoradiation. Ann Oncol 17: 1103-1110, 2006

27. Chau I, Allen M, Cunningham D, et al: Neoadjuvant systemic fluorouracil and mitomycin C prior to synchronous chemoradiation is an effective strategy in locally advanced rectal cancer. Br J Cancer 88: 1017-1024, 2003

28. Glynne-Jones R, Grainger J, Harrison M, et al: Neoadjuvant chemotherapy prior to preoperative chemoradiation or radiation in rectal cancer: Should we be more cautious? Br J Cancer 94:363-371, 2006

29. Machiels JP, Aydin S, Bonny MA, et al: What is the best way to predict disease-free survival after preoperative radiochemotherapy for rectal cancer patients: Tumor regression grading, nodal status, or circumferential resection margin invasion? J Clin Oncol 24:1319, 2006

30. Fietkau R, Barten M, Klautke G, et al: Postoperative chemotherapy may not be necessary for patients with ypN0-category after neoadjuvant chemoradiotherapy of rectal cancer. Dis Colon Rectum 49:1284-1292, 2006

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

ERRATA

The November 1, 2006, article by Cai et al entitled, "Prospective Study of Urinary Prostaglandin E_2 Metabolite and Colorectal Cancer Risk" (J Clin Oncol 24:5010-5016, 2006) contained an error. In Table 3, the 95% CI for the fourth PGE-M quartile of Rectal cancer was given as 1.7 to 3.7, whereas it should have been 1.7 to 30.7.

DOI: 10.1200/JCO.2007.12.1301

The January 1, 2007 article by Kondagunta et al entitled, "Paclitaxel Plus Ifosfamide Followed by High-Dose Carboplatin Plus Etoposide in Previously Treated Germ Cell Tumors" (J Clin Oncol 25:85-90, 2007) presented inaccurate results in Figure 2, which should have shown that 51% of patients survived. The corrected figure is reprinted below in its entirety. The online version has been corrected in departure from the print.

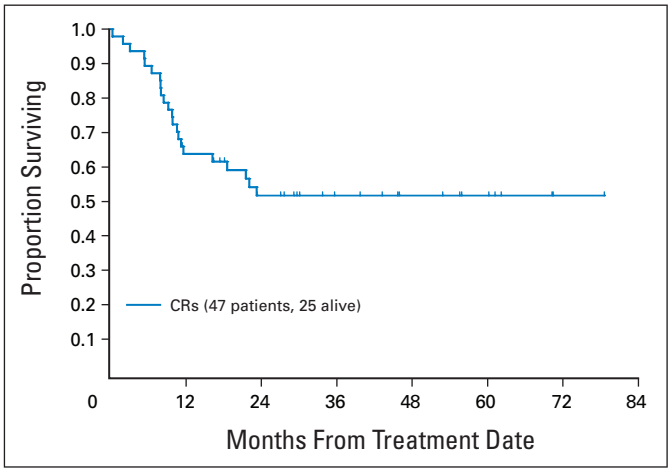

Fig 2. Overall survival curve. Tick marks indicate last follow-up.

DOI: 10.1200/JCO.2007.12.1335

The January 1, 2007 article by Rödel et al entitled, "Multicenter Phase II Trial of Chemoradiation With Oxaliplatin for Rectal Cancer" (J Clin Oncol 25:110-117, 2007) contained an error. The affiliation for Alois Fürst was given as Department of Surgery, Caritas-Hospital St Josef, Regensburg, Germany; whereas it should have been Department of General Surgery, University of Regensburg, Regensburg, Germany.

DOI: 10.1200/JCO.2007.12.1319