Overview

The Oncologist®
The official journal of the Society for Translational Oncology

First Published Online September 10, 2014

DOI: 10.1634/theoncologist.2014-0233

Title: Preoperative Chemotherapy in Patients With Intermediate-Risk Rectal Adenocarcinoma Selected by High-Resolution Magnetic Resonance Imaging: The GEMCAD 0801 Phase II Multicenter Trial

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ClinicalTrials.gov Identifier: NCT00909987

Sponsor(s): Gemcad Group

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IRB Approved: Yes

Disclosures

Gina Brown: Royal Marsden Hospital National Institute for Health Research Biomedical Research Centre (RF); **Vicente Alonso:** Roche, Merck-Serono (C/A); **Miguel Pera:** Ethicon, Inc. (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background
The need for preoperative chemoradiation or short-course radiation in all T3 rectal tumors is a controversial issue. A multicenter phase II trial was undertaken to evaluate the efficacy and safety of neoadjuvant capecitabine and oxaliplatin combined with bevacizumab in patients with intermediate-risk rectal adenocarcinoma.

Methods
We recruited 46 patients with T3 rectal adenocarcinoma selected by magnetic resonance imaging (MRI) who were candidates for (R0) resection located in the middle third with clear mesorectal fascia and who were selected by pelvic MRI. Patients received four cycles of neoadjuvant capecitabine and oxaliplatin combined with bevacizumab (final cycle without bevacizumab) before total mesorectal excision (TME). In case of progression, preoperative chemoradiation was planned. The primary endpoint was overall response rate (ORR).

Results

On an intent-to-treat analysis, the ORR was 78% (n = 36; 95% confidence interval [CI]: 63%–89%) and no progression was detected. Pathologic complete response was observed in nine patients (20%; 95% CI: 9–33), and T downstaging was observed in 48%. Forty-four patients proceeded to TME, and all had R0 resection. During preoperative therapy, two deaths occurred as a result of pulmonary embolism and diarrhea, respectively, and one patient died after surgery as a result of peritonitis secondary to an anastomotic leak (AL). A 13% rate of AL was higher than expected. The 24-month disease-free survival rate was 75% (95% CI: 60%–85%), and the 2-year local relapse rate was 2% (95% CI: 0%–11%).

Conclusion

In this selected population, initial chemotherapy results in promising activity, but the observed toxicity does not support further investigation of this specific regimen. Nevertheless, these early results warrant further testing of this strategy in an enriched population and in randomized trials.

Discussion

To the best of our knowledge, this is the first multicenter phase II trial evaluating neoadjuvant systemic therapy without radiation in rectal cancer. The high-quality staging procedure with a central reviewer in this trial ensured a very homogeneous population. Early trials on rectal cancer have no validated early endpoints that could serve as surrogates for long-term outcome [1]. Consequently, we used radiological overall response rate (ORR) as the primary endpoint in this study. Response Evaluation Criteria In Solid Tumors quantification of the response correlated with survival in early clinical trials [2]. Furthermore, due to the particular design of this trial, the radiological restaging allowed us to capture the specific efficacy of neoadjuvant capecitabine and oxaliplatin combined with bevacizumab (CAPOX-B), The incidence of grade 3–4 adverse events was similar to that reported for this regimen in large phase III trials [3,], but the rate of anastomotic leak (AL; 13%) was higher than expected. Although the findings have not been uniform, phase II trials combining preoperative bevacizumab with chemotherapy and/or chemoradiation for locally advanced rectal cancer have revealed an increased rate of wound complications [4]. We also observed a high frequency (6%) of fatal adverse events. Two of the three deaths (i.e., one massive pulmonary thromboembolism in an 84-year-old man and one peritonitis secondary to AL) were attributable, at least in part, to bevacizumab.

The ORR was 78% after preoperative CAPOX-B, and because no disease progression was observed, no patient received preoperative chemoradiation (CRT). The R0 resection rate was 100%, and the pathological complete response (pCR) rate was 20%. Although the rate of local relapse (LR) is just 2%, these data must be interpreted with caution because follow-up is short for this endpoint. Our early efficacy endpoints (Table 1) and the low rate of LR were similar to those recently reported by Scrhag et al. [5]; however, the observed mortality in our series was higher. Although both studies have a similar approach, the investigators from Memorial Sloan Kettering Cancer Center used bevacizumab combined with FOLFOX in a single-center trial, and that may, at least in part, explain the differences. In addition, our efficacy results seem very similar to those observed in patients randomly assigned to combined preoperative fluoropyrimidines and radiation in recently published phase III trials. In the German CAO/ARO/AIO-04 [6] trial with a population composed mainly of stage cT3 tumors (84%), pCRs were achieved in 13% of patients who underwent surgery in the 5-fluorouracil/RT group, with ypN0 of 69%.

A limitation of our trial is patient selection. Increases in thromboembolic events have been described in older patients treated with bevacizumab [7]. Consequently, careful patient selection remains important and is a major concern for this potentially curable population.

In summary, the observed toxicity does not warrant further investigation of this specific regimen, but our findings provide justification for additional investigation of this strategy. The phase II/III Alliance for Clinical Trials in Oncology trial (NCT01515787) is under way and will compare neoadjuvant FOLFOX with selective CRT versus standard preoperative CRT.

Trial Information

Disease	Colorectal cancer
Stage of disease / treatment	Neoadjuvant
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Overall Response Rate

Additional Details of Endpoints or Study Design	Secondary endpoints included pathologic complete response, downstaging, R0 resection rate, and safety
Investigator's Analysis	Active but too toxic as administered in this study

Drug Information

Drug 1 **Generic/Working name**	Capecitabine
Trade name	Xeloda
Company name	Roche
Drug type	Other
Drug class	Antimetabolite
Dose	2,000 mg/m^2
Route	Oral (po)
Schedule of Administration	4 cycles of CAPOX and bevacizumab every 3 weeks. Last cycle did not include bevacizumab. Bevacizumab 7.5 mg/kg i.v. Oxaliplatin 130 mg/m^2 i.v. (2-hour infusion), capecitabine 2,000 mg/m^2 twice per day on days 1–14 of a 3-week cycle
Drug 2 **Generic/Working name**	Oxaliplatin
Trade name	Eloxatin
Company name	Sanofi
Drug type	Other
Drug class	Alkylating agent
Dose	130 mg/m^2
Route	IV
Drug 3 **Generic/Working name**	Bevacizumab
Trade name	Avastin
Company name	Roche
Drug type	Antibody
Drug class	VEGF
Dose	7.5 mg/kg
Route	IV
Schedule of Administration	

Patient Characteristics

Number of patients, male	28
Number of patients, female	18
Stage	Clinical stage II and stage III
Age	Median (range): 61 (32–82)
Number of prior systemic therapies	Median (range): 0
Performance Status:	ECOG 0 — 35 1 — 10 2 — 3 — unknown — 1
Other	Not collected
Cancer Types or Histologic Subtypes	Adenocarcinoma 46

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened	70
Number of patients enrolled	46
Number of patients evaluable for toxicity	46
Number of patients evaluated for efficacy	40
Evaluation method	Other
Response assessment CR	11%
Response assessment PR	67%
Response assessment SD	7%
Response assessment PD	0%
Response assessment other	15%

Adverse Events

Adverse event	*n*	%
Grade 3/4	28	61
Any grades adverse event	2	4
Neutropenia	7	15
Diarrhea	2	4
Hand-foot	2	4
Thromboembolic	1	2
Hypertension	1	2
Gastrointestinal perforation	3	7
Hypersensitivity	1	2
Cardiac ischemia	2	4
Death	2	4
Diarrhea/renal failure	1	2
Pulmonary embolism	1	2
30-day surgical complication		
Anastomotic leak	6	13
Infection and wound healing	3	7
Stoma complications	1	2
Reoperation	3	7
Death (anastomotic leak and peritonitis)	1	2

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Not collected
Investigator's Assessment	Active but too toxic as administered in this study

Discussion

The need for preoperative radiation in stage T3 rectal cancer has long been debated [8] because retrospective data suggest it may not be needed in all patients with stage II/III rectal cancer [9], and pelvic radiation is associated with an increased incidence of serious late morbidity [10]. Furthermore, the MERCURY study group recently reported that in good-prognosis tumors (i.e., magnetic resonance imaging-predicted [MRI-predicted] safe circumferential resection margins) treated with good-quality total mesorectal excision (TME) surgery, the local relapse (LR) rate at 5 years was just 3%, even when including some patients with node-positive disease; however, the distant relapse rate at 5 years was 20% [11].

Based on these observations, we hypothesized that modern neoadjuvant chemotherapy alone offers an attractive alternative approach because it can be an effective local treatment that also allows early treatment of micrometastases at therapeutic doses without the long-term side effects of radiation. These attributes are valuable in a rectal cancer population in which the risk of metastatic disease predominates over the risk of local recurrence.

Data from a study by Willett et al. involving patients with locally advanced rectal (LAR) cancer demonstrated antivascular and normalizing effects of vascular endothelial growth factor blockade with bevacizumab in these tumors and encouraging activity when combined with chemotherapy and radiation, with acceptable acute and postoperative toxicity [12].

With this background, we initiated a phase II trial to evaluate whether neoadjuvant capecitabine and oxaliplatin combined with bevacizumab (CAPOX-B) results in radiological and pathological responses in patients with MRI-detected T3 rectal adenocarcinoma who were candidates for (R0) resection located in the middle third with clear mesorectal fascia and who were selected by pelvic MRI.

The MRI criteria for intermediate cancer were as follows: tumor stage T3 (i.e., tumor invades subserosa through muscularis propria) with distal border of tumor $>$5 cm from the anal verge and below the sacral promontory and predicted clear mesorectal fascia defined as $\geq$2 mm from tumor to fascia.

Eligible patients were managed with neoadjuvant therapy with four cycles of CAPOX-B, but the fourth cycle of therapy did not include bevacizumab. Patients underwent restaging with MRI scans of the pelvis within 3–4 weeks of their fourth cycle. All pre- and post-treatment MRI scans were reviewed independently by one radiologist (G.B.). Patients without progression proceeded to TME 4–6 weeks after the last chemotherapy dose. Standardized pathology examinations and the plane of surgery achieved were performed by using the method of Quirke et al. [13, 14]. Pathological complete response (pCR) was defined as the absence of viable tumor cells in the primary tumor and in the lymph nodes (ypT0N0). Chemoradiation (CRT) was planned before surgery for patients with progressive disease during or after neoadjuvant chemotherapy; for those who were not candidates for R0 resection; or for those who, after surgery, had a circumferential resection margin positive or had N2 nodal metastases. The primary endpoint was radiologic overall response rate (ORR; CR plus partial response [PR]). A MinMax two-stage design, as proposed by Simon [15], was used. An ORR rate of 60% was considered acceptable (p1), and an ORR rate of 40% would be ruled out as unacceptable (p0). pCR was also an important consideration. It was required that at least 6 of the 46 patients (13%) achieve pCR with this neoadjuvant regimen. Following Simon's MinMax methodology, the probability of observing at least 6 pCRs is $>$80% if the true CR rate is 20%. Estimates used in the formulation of these hypotheses were derived from response rates to CAPOX-B in metastatic colorectal cancer [3] and pCR with standard chemoradiation in recent large trials [6, 10]. With a sample size of 41 patients (type I error $\alpha = 0.1$ and type II error $\beta = 0.1$; 90% power), the treatment would be considered suitable for further evaluation if $\geq$21 patients achieved CR or PR. The planned patient number was increased to 46 to allow for a 10% dropout rate. Figure 1 shows the progression of all patients during the trial. The cutoff date for this report was March 2014. The demographic and baseline MRI characteristics of the 46 patients are provided in Table 1. Of the 46 patients who started treatment, 39 (85%) received all four cycles. The mean relative dose intensity of capecitabine, oxaliplatin, and bevacizumab was 0.89, 0.96, and 0.98, respectively. No patient received CRT in the neoadjuvant period.

Table 2 lists the radiological response and other early efficacy parameters. With a median follow-up time of 30.2 months, the 24-month disease-free survival rate was 75% (95% confidence interval [CI]: 60%–85%). The 24-month overall survival rate was 91% (95% CI: 78%–96%) (Fig. 2). Overall, 11 patients experienced relapse (1 local and 10 distant).

Table 3 lists the adverse events associated with CAPOX-B. Anastomotic leaks (AL) were detected in 6 patients (13%), and 3 required reoperation. One of these patients died as a result of peritonitis. Although in this trial surgery took place at least 6 weeks after the last bevacizumab dose, which is considered a conservative approach, the relatively high AL rates may be attributable in part to bevacizumab. We had an unacceptable incidence of fatal adverse events. Two patients died in the induction period after the second cycle, one from a massive pulmonary thromboembolism in a patient aged 82 years. Another patient died of diarrhea leading to multiorgan failure, and one patient died in the 30-day postoperative period after peritonitis secondary to AL. Consequently, for further development in future trials, it would be important to develop risk-reduction strategies with this approach that should include selection of appropriate patients for therapy, early assessment of toxic effects, adequate management of serious adverse events, and capecitabine dose reduction

The study met the efficacy goals, (i.e., ORR and pCR), and these seem similar to those observed in this population after combined fluoropyrimidines and radiation. The low rate of LR is also a reflection of improvements in surgical quality

demonstrated in this trial, with 1 of 40 poor-grade specimens. This has unmasked the problem of systemic control (20% distant relapses at 2 years) that is now emerging as the major challenge in this population. In conclusion, although the observed toxicity does not warrant further investigation of this specific regimen, our findings provide justification for additional investigation of this strategy.

Acknowledgments

We thank the patients and study investigators; Patricia Romero, Paz Torres, and Dolores Ferrandez (Roche); and José Javier Garcia and his team (Pivotal) for statistical advice and monitoring support.

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Figures and Tables

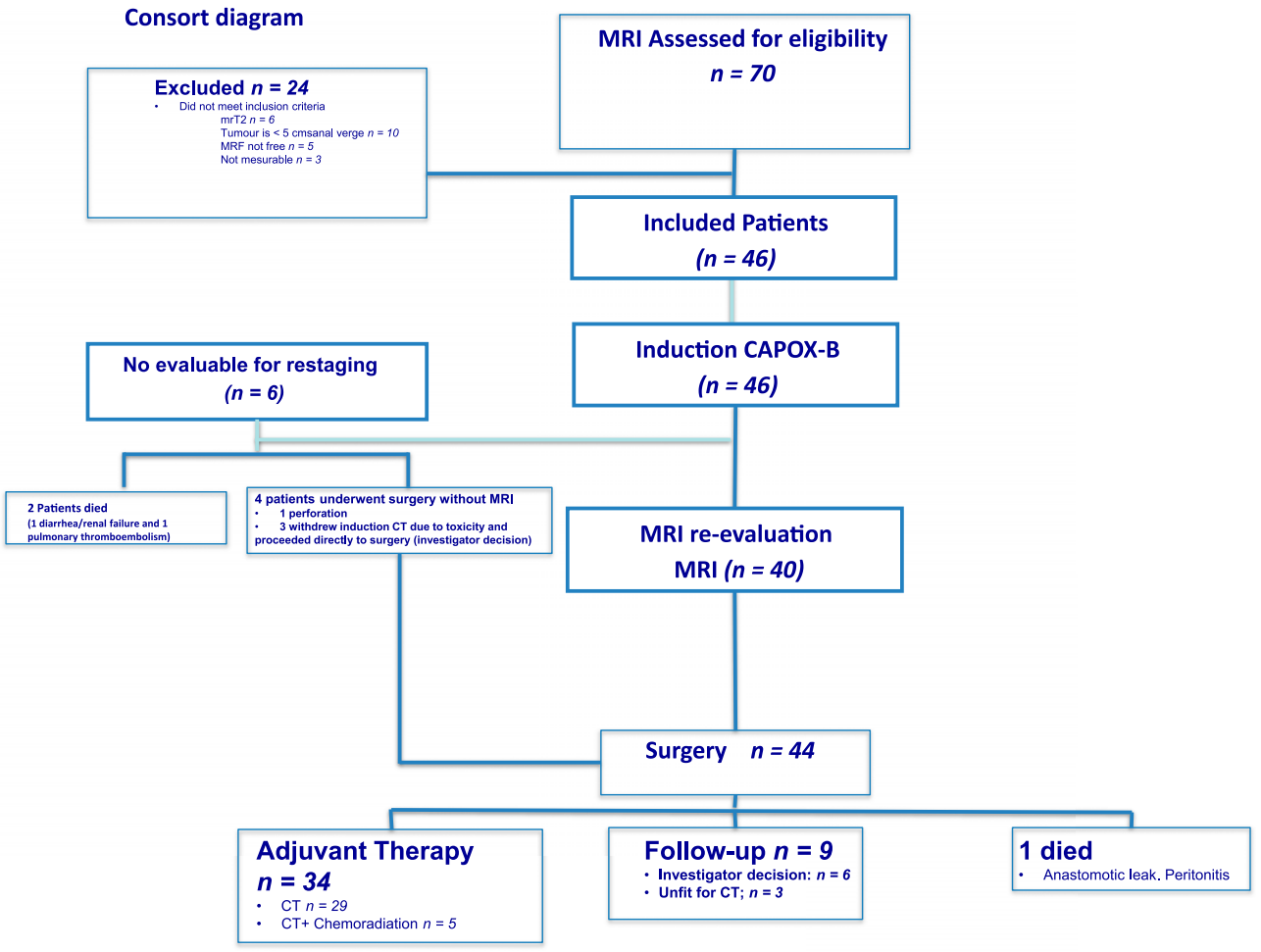
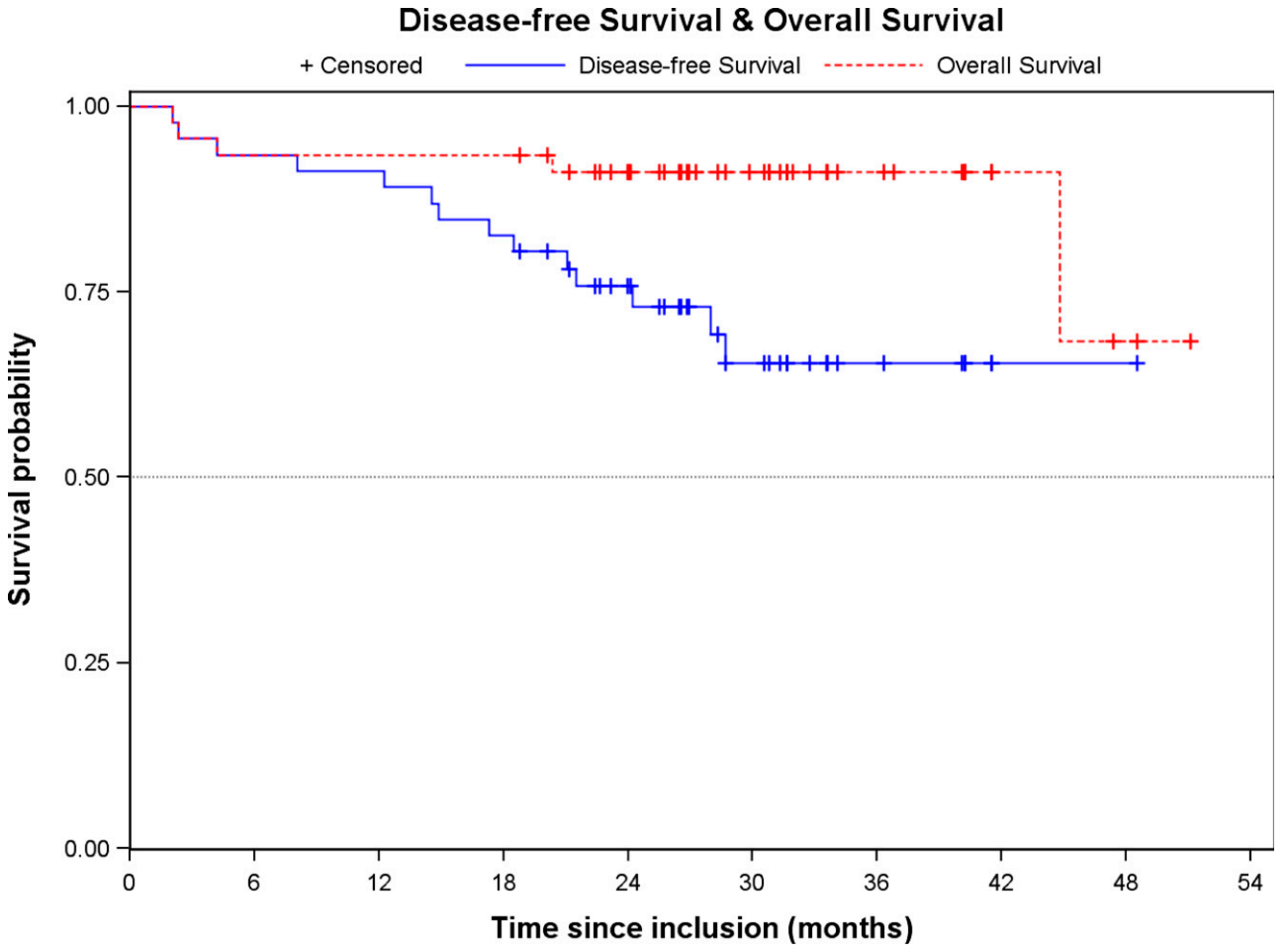


Figure 1. Consort diagram.
Abbreviations: CT, chemotherapy; MRI, magnetic resonance imaging.



Strata	Subjects	Event	% Events	Censored	% Censored	Median	CI 95% LL	CI 95% UL
Disease-free Survival	46	14	30.4	32	69.6	.	28.7	.
Overall Survival	46	5	10.9	41	89.1	.	44.8	.

Figure 2. Disease-free survival and overall survival for all eligible patients ($n = 46$).
Abbreviations: CI, confidence interval; LL, lower level; UL, upper level.

Table 1. Demographics

Characteristic ($n = 46$)	Result
Age, years	
Median	61
Range	32–82
Sex, *n* (%)	
Male	28 (61)
Female	18 (39)
Inclusion criteria as defined by MRI, *n* (%)	
Distal margin from tumor >5 cm to anal verge and under promontory	46 (100)
MRF free (tumor ≥2 mm from MRF)	46 (100)
mrT3	45 (98)
mrT3 and EMVI absent	12(26)
mrT3 and EMVI present	33 (72)
mrT4 (peritoneal reflection positive, MRF free) and EMVI present	1 (2)
N staging as defined by MRI, *n* (%)	
mrN0 (Nodes show homogenous signal and no capsular breach by tumor)	18 (39)
mrN1	19 (41)
mrN2	8 (18)
Missing	1 (2)

Abbreviations: EMVI, extramural venous invasion; mr, MRI-derived; MRF, mesorectal fascia; MRI, magnetic resonance imaging.

Table 2. Radiological and pathological response

Response	Result
Primary endpoint: objective tumor response by MRI, ITT population ($n = 46$)	
Overall response	36 (78); 95% CI: 63–89
mr complete response	5 (11)
mr partial response	31 (67)
mr stable disease	3 (7)
mr not evaluable	1 (2)
Missing	6 (13)
Secondary endpoints: pathologic response, ITT population ($n = 46$)	
pCR (ypT0N0)	9 (20); 95% CI: 9.4–33.9
T downstaging	22 (48)
N downstaging	15 (56)[a]
TRG 4, complete regression	9 (20)
TRG 3, >50% of tumor mass	10 (22)
TRG 2, ≥25% to 50% of tumor mass	11 (24)
TRG 1, <25% of tumor mass	7 (15)
TRG 0, no regression	7 (15)

ypN0	31 (67)
ypN1	10 (21)
ypN2	3 (7)
Quality of surgery ($n = 44$)	
CRM free	42 (95)
R0 resection rate	44 (100)
Good TME quality[b]	40 (91)

Data are shown as *n* (%) unless otherwise indicated. T downstaging defined as lower pathologic T stage compared with the pretreatment mrT stage. N downstaging defined as N negative pathologic stage compared with mrN positive at baseline.
[a]15 ypN negative of 29 mrN positive at baseline.
[b]Defined as intact mesorectum with only minor irregularities.
Abbreviations: CRM, circumferential resection margin; ITT, intention to treat; mr, magnetic resonance; pCR, pathological complete response; TME: total mesorectal excision; TRG: tumor regression grade.

Table 3. Adverse events

Adverse event	***n***	**%**
Grade 3/4	28	61
Any grades adverse event	2	4
Neutropenia	7	15
Diarrhea	2	4
Hand-foot	2	4
Thromboembolic	1	2
Hypertension	1	2
Gastrointestinal perforation	3	7
Hypersensitivity	1	2
Cardiac ischemia	2	4
Death	2	4
Diarrhea/renal failure	1	2
Pulmonary embolism	1	2
30-day surgical complication		
Anastomotic leak	6	13
Infection and wound healing	3	7
Stoma complications	1	2
Reoperation	3	7
Death (anastomotic leak and peritonitis)	1	2