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Multicenter Randomized Phase II Clinical Trial Comparing Neoadjuvant Oxaliplatin, Capecitabine, and Preoperative Radiotherapy With or Without Cetuximab Followed by Total Mesorectal Excision in Patients With High-Risk Rectal Cancer (EXPERT-C)

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ABSTRACT

Purpose
To evaluate the addition of cetuximab to neoadjuvant chemotherapy before chemoradiotherapy in high-risk rectal cancer.

Patients and Methods
Patients with operable magnetic resonance imaging–defined high-risk rectal cancer received four cycles of capecitabine/oxaliplatin (CAPOX) followed by capecitabine chemoradiotherapy, surgery, and adjuvant CAPOX (four cycles) or the same regimen plus weekly cetuximab (CAPOX+C). The primary end point was complete response (CR; pathologic CR or, in patients not undergoing surgery, radiologic CR) in patients with *KRAS*/*BRAF* wild-type tumors. Secondary end points were radiologic response (RR), progression-free survival (PFS), overall survival (OS), and safety in the wild-type and overall populations and a molecular biomarker analysis.

Results
One hundred sixty-five eligible patients were randomly assigned. Ninety (60%) of 149 assessable tumors were *KRAS* or *BRAF* wild type (CAPOX, n = 44; CAPOX+C, n = 46), and in these patients, the addition of cetuximab did not improve the primary end point of CR (9% *v* 11%, respectively; $P = 1.0$; odds ratio, 1.22) or PFS (hazard ratio [HR], 0.65; $P = .363$). Cetuximab significantly improved RR (CAPOX *v* CAPOX+C: after chemotherapy, 51% *v* 71%, respectively; $P = .038$; after chemoradiation, 75% *v* 93%, respectively; $P = .028$) and OS (HR, 0.27; $P = .034$). Skin toxicity and diarrhea were more frequent in the CAPOX+C arm.

Conclusion
Cetuximab led to a significant increase in RR and OS in patients with *KRAS/BRAF* wild-type rectal cancer, but the primary end point of improved CR was not met.

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INTRODUCTION

Surgery remains the primary determinant of cure in patients with localized rectal cancer, and total mesorectal excision (TME) is now widely accepted as standard of care.[1,2] Early-stage rectal cancer (TNM T1-T2N0M0) is associated with 5-year survival rates greater than 90% after surgery alone; therefore, neoadjuvant treatment is reserved for locally advanced disease. High-resolution magnetic resonance imaging (MRI) is routinely used to stage and identify high-risk features in rectal cancers, including a potentially positive circumferential resection margin, extramural venous invasion, and extramural spread beyond 5 mm. Identification of these features, which predict high risk of local or systemic relapse, enables appropriate selection of patients for neoadjuvant treatment.[3-6]

The widespread implementation of neoadjuvant short-course radiotherapy or long-course chemoradiotherapy (CRT) has reduced local recurrence rates from 25% to 40% to less than 10%; however, only the Swedish Rectal Cancer Trial demonstrated an overall survival (OS) benefit. Despite low local relapse rates, systemic recurrence remains a significant problem, occurring in 30% to 40% of patients.[7,8]

Intensification of CRT with the addition of oxaliplatin to fluoropyrimidine-based CRT demonstrated improved pathologic complete response (pCR)

rates in phase II trials[9-12]; however, these results have not been replicated in phase III trials. To date, the ACCORD 12/0405/Prodige 2 (Partenariat de Recherche en Oncologie Digestive 2),[13] STAR (Studio Terapia Adiuvante Retto),[14] and National Surgical Adjuvant Breast and Bowel Project R-04 trials[15] have failed to demonstrate benefit from addition of oxaliplatin to CRT, and all reported increased rates of grade 3 and 4 toxicity. Only the CAOI/ARO/AIO-04 trial demonstrated improvements in pCR (12.8% with CRT *v* 16.5% with CRT and oxaliplatin; $P = .045$) with addition of oxaliplatin in an unplanned exploratory analysis.[16]

Preclinical evidence suggests that cetuximab is a potent radiosensitizer, and cetuximab-based radiotherapy in patients with locally advanced head and neck cancer improved locoregional control and OS compared with radiotherapy alone.[17] Addition of cetuximab to CRT in rectal cancer has subsequently been assessed in several phase II studies[18-25] with acceptable pCR rates and manageable toxicity.[26]

Although the rationale for neoadjuvant chemotherapy includes downstaging of the primary tumor and improved curative resection rates, potential exists to reduce distant recurrence through early initiation of systemic treatment. Oxaliplatin in combination with fluoropyrimidine-based chemotherapy has resulted in improved response rates, progression-free survival (PFS), and OS in metastatic colorectal cancer[27,28] and survival benefit in the adjuvant setting.[29] We previously demonstrated the feasibility of administering neoadjuvant oxaliplatin and capecitabine (CAPOX) before CRT and TME in patients with poor prognosis rectal cancer in a single-arm phase II trial (EXPERT).[30] Patients received four cycles of CAPOX followed by capecitabine CRT, TME, and 12 weeks of adjuvant capecitabine. Radiologic response (RR) rates were 74% after neoadjuvant chemotherapy and 89% after CRT, with a pCR rate of 20%. Five-year PFS and OS rates were 64% and 75%, respectively, despite the poor-risk population. Addition of cetuximab to oxaliplatin-based chemotherapy enhances response rate in the metastatic setting, and this may translate to higher complete resection and pCR rates when cetuximab is added to neoadjuvant treatment (EXPERT-C). In light of emerging data demonstrating *KRAS*/*BRAF* mutations as predictive for lack of response to anti–epidermal growth factor receptor (EGFR) therapy in metastatic colorectal cancer,[31,32] the primary end point was analyzed in *KRAS*/*BRAF* wild-type tumors.

PATIENTS AND METHODS

Patients

Eligible patients had histologically confirmed high-risk operable rectal adenocarcinoma. High-risk disease was defined by presence of at least one of the following on high-resolution thin-slice MRI (3 mm): tumor within 1 mm of mesorectal fascia, T3 tumor at or below levators, extramural extension ≥ 5 mm, T4 tumor, or presence of extramural venous invasion.

All patients had WHO performance status of 0 to 2 with no metastatic disease. Other inclusion criteria were as follows: age ≥ 18 years; adequate bone marrow, renal, and liver function; life expectancy more than 3 months; no concurrent uncontrolled medical condition; and no active malignant disease other than nonmelanotic skin cancer or carcinoma in situ of the uterine-cervix in the last 10 years. Written informed consent was obtained from each patient before study entry.

Procedures

Both arms included neoadjuvant chemotherapy with CAPOX followed by capecitabine CRT, TME, and adjuvant CAPOX. Patients were randomly assigned in a 1:1 ratio to receive weekly cetuximab with chemotherapy (CAPOX+C) and CRT or the control treatment (CAPOX). Stratification was according to treatment center and the presence or absence of T4 disease.

Neoadjuvant chemotherapy. Four cycles of chemotherapy were administered; oxaliplatin (130 mg/m^2) was administered intravenously on day 1, and capecitabine was administered in two divided oral doses on days 1 through 14, every 21 days. The capecitabine dose was reduced from 2,000 to 1,700 mg/m^2 in line with data from the TREE-2 (Three Regimens of Eloxatin Evaluation) study[33] after four of the first 14 patients developed grade 3 diarrhea requiring hospitalization. Patients randomly assigned to CAPOX+C received a loading dose of cetuximab 400 mg/m^2 on day 1 followed by 250 mg/m^2/wk. Doses were capped at a body-surface area of 2 m^2, and patients age ≥ 75 years received capecitabine (1,300 mg/m^2/d) and oxaliplatin (100 mg/m^2). Dose adjustment was made according to observed toxicity, which was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Because of increased rates of thromboembolic events in the early stages of the EXPERT trial (8%),[30] all patients received prophylactic low molecular weight heparin during neoadjuvant chemotherapy.

Synchronous CRT. Radiation was conformally computed tomography (CT) planned and delivered in a two-phase technique (phase 1, 45 Gy in 25 fractions encompassing the primary tumor and pelvic lymph nodes; phase 2, 5.4 Gy in 3 fractions to the assessable tumor with a 2-cm margin in all directions). Concomitant capecitabine 1,650 mg/m^2/d was administered with or without cetuximab 250 mg/m^2 weekly during the radiotherapy. Dose adjustment was made according to observed toxicity, which was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events and Radiation Therapy Oncology Group score 1 to 4.

Surgery. TME, as described by Heald and Ryall,[1] was performed 4 to 6 weeks after completion of CRT, unless postchemoradiation imaging demonstrated inoperable tumor or metastatic disease.

Adjuvant treatment. Adjuvant treatment commenced 6 to 8 weeks after surgery. Patients received four cycles of chemotherapy identical to the neoadjuvant phase.

A CT scan of the thorax and abdomen and an MRI scan of the pelvis were repeated after each phase of treatment. MRI scans were reviewed centrally by one radiologist blinded to treatment arm and reported in accordance with RECIST. Toxicity and adverse event assessments were performed before each treatment cycle and repeated at the end of each phase of treatment. Quality-of-life questionnaires were completed using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (version 3.0) during weeks 6 and 12 of neoadjuvant chemotherapy and after CRT. Histopathology was assessed as described by Quirke et al,[34] and pCR was defined as the absence of any residual tumor cells detected in the resected specimen. Resection specimens were examined for margin involvement, which was defined as tumor observed ≤ 1 mm from the margins of the surgical specimen. Follow-up carcinoembryonic antigen measurements were done every 3 months in year 1, every 6 months in years 2 and 3, and annually in years 4 and 5. A CT scan of the thorax, abdomen, and pelvis was performed at 12, 24, and 36 months, and an MRI of the pelvis was performed at 24 months.

Molecular Analysis

Mutational analysis of *KRAF* and *BRAF* was performed centrally on genomic DNA extracted from formalin-fixed, paraffin-embedded tissue slides or sections with the use of the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). *KRAS* and *BRAF* mutations were analyzed in the biopsy and primary resection samples using the INFINITI platform (AutoGenomics, Vista, CA), as per the manufacturer's instructions. *PIK3CA* mutational analysis was performed with direct gene sequencing, and PTEN status was determined by immunohistochemistry using the PTEN antibody 6H2.1 (Cascade Bioscience, Winchester, MA). PTEN expression was scored semiquantitatively by a single pathologist using light microscopy and normal endothelial cells as an internal positive control. The intensity of cytoplasmic staining was documented (0, 1, 2, or 3), and tumors were then classified as PTEN negative (0) or PTEN positive (1 to 3). A bright-field dual in situ hybridization assay of *EGFR* was performed, and increased *EGFR* gene copy number was defined using the Colorado scoring system.[35] NRAS mutations in codons 12, 13, and 61 were analyzed using multiplex polymerase chain reaction.

Statistical Considerations

The trial was originally designed to detect a 20% improvement in pCR; however, after the *KRAS* and *BRAF* data,[31,32] the protocol was amended to analyze the primary end point of complete response (CR; pCR or, in patients who did not undergo surgery, radiologic CR) in patients with *KRAS*/*BRAF* wild-type tumors. With 165 patients, approximately 50 patients with *KRAS*/*BRAF* wild-type tumors were expected in each arm, allowing detection of an odds ratio (OR) of 3.4 with a two-sided α of 5% and 80% power.

Secondary end points were CR in the all treated patients, RR, PFS, OS, safety, and quality of life. PFS was measured from date of random assignment to date of disease progression, relapse, or death from any cause, and OS was calculated from time of random assignment to date of death from any cause or last visit. Patients without an event were censored at last follow-up. Comparison of the treatment arms was carried out using a log-rank analysis. The Kaplan-Meier method was used to estimate OS and PFS, and these analyses were repeated in the unselected all-treated and *KRAS/BRAF* wild-type populations. The frequency of *PIK3CA* and *NRAS* mutations, *EGFR* gene copy number, and PTEN expression were also determined.

RESULTS

Between October 2005 and July 2008, 165 patients were randomly assigned from 15 European centers to CAPOX+C (n = 84) or CAPOX (n = 81). One patient was ineligible (Fig 1). Baseline charac-

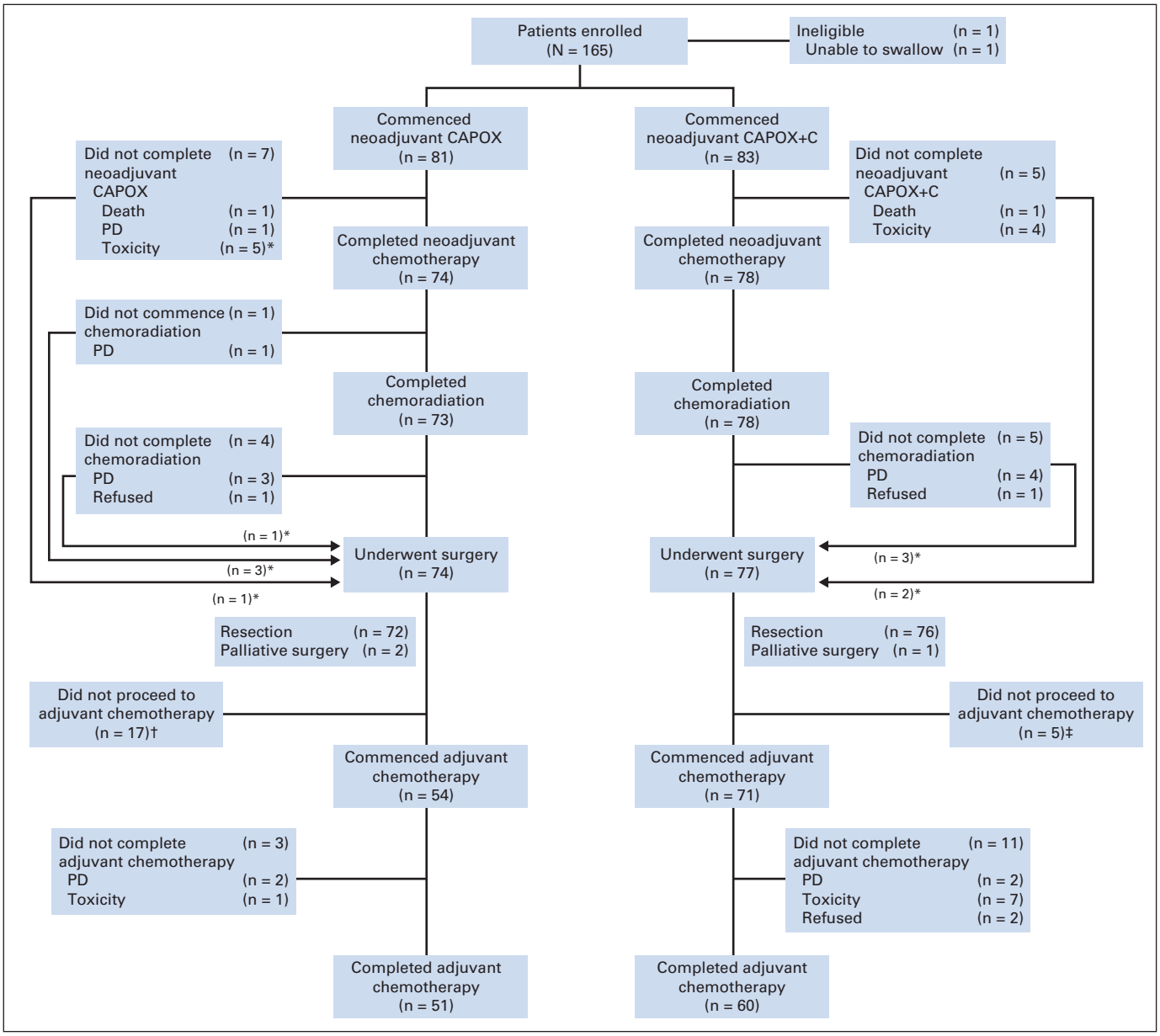

Fig 1. Consort diagram. (*) Patients who had progressive disease (PD) or toxicity but proceeded to next step. (†) Reasons for not proceeding included the following: liver metastases at surgery (n = 1), second primary tumor at surgery (n = 1), perioperative death (n = 2), PD/death (n = 1), poor healing (n = 1), postoperative complication (n = 5), refused (n = 4), PD after neoadjuvant therapy (n = 2), and neoadjuvant chemotherapy toxicity (n = 1). (‡) Reasons for not proceeding included the following: PD/death (n = 1), refused (n = 2), cerebrovascular accident (n = 1), and renal failure (n = 1). CAPOX, capecitabine/oxaliplatin; CAPOX+C, capecitabine/oxaliplatin plus cetuximab.

Table 1. Baseline Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	CAPOX				CAPOX+C			
	All Treated Patients (n = 81)		Wild-Type Patients (n = 44)		All Treated Patients (n = 83)		Wild-Type Patients (n = 46)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	47	58	23	52	54	65	31	67
Female	34	42	21	48	29	35	15	33
Age, years								
Median	65		63		61		59	
Range	28-79		28-79		31-75		31-75	
Performance status								
0	39	48	22	50	39	47	23	50
1	41	51	22	50	42	51	21	46
2	1	1	0		2	2	2	4
MRI-defined high-risk features								
T3c-T3d	56	69	33	75	47	57	23	50
T4	19	23	11	25	21	25	12	26
CRM involved/at risk	45	56	25	57	48	58	26	57
EMVI positive	60	74	33	75	58	70	32	72
Low-lying tumor (at/below levators)	38	47	20	45	39	47	32	48

Abbreviations: CAPOX, capecitabine/oxaliplatin; CAPOX+C, capecitabine/oxaliplatin plus cetuximab; CRM, circumferential resection margin; EMVI, extramural venous invasion; MRI, magnetic resonance imaging.

Table 3. Radiologic Response

Response	Wild-Type Patients					All Treated Patients				
	CAPOX (n = 44)		CAPOX+C (n = 46)			CAPOX (n = 81)		CAPOX+C (n = 83)		
	No.	%	No.	%	P	No.	%	No.	%	P
Neoadjuvant chemotherapy										
CR	1	2	5	11		2	3	6	8	
PR	21	48	27	59		38	51	43	56	
SD	20	46	12	26		33	44	27	35	
PD	1	2	0	0		2	3	1	1	
Unknown*	1	2	2	4		6	7	6	7	
Overall response†	22	51	32	71	.038	40	54	49	64	.41
Chemoradiation										
CR	2	5	7	16		7	9	9	11	
PR	30	70	34	77		50	66	55	72	
SD	6	14	3	7		14	19	11	14	
PD	4	9	0	0		4	5	1	1	
Unknown*	1	2	2	4		6	8	7	8	
Overall response†	32	75	41	93	.065	57	76	64	84	.23

Abbreviations: CAPOX, capecitabine/oxaliplatin; CAPOX+C, capecitabine/oxaliplatin plus cetuximab; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
*Patients for whom no best response was provided by the investigator.
†Overall response = CR+PR.

teristics were balanced between the treatment arms (Tables 1 and 2), and the majority of patients had more than one high-risk factor. The analysis was performed after median follow-up times of 37 months (CAPOX+C) and 32 months (CAPOX), once the molecular analysis was complete.

Of 164 eligible patients, molecular analysis for *KRAS*/*BRAF* was successfully performed in 149 patients. There was insufficient tissue for molecular analysis in 15 patients (as a result of pCR in eight patients). Sixty percent of patients (90 of 149 patient) had *KRAS*/*BRAF* wild-type tumors (CAPOX+C, n = 46; CAPOX, n = 44).

Table 2. Molecular Characteristics

Molecular Characteristic	CAPOX		CAPOX+C		All Patients	
	No./Total No.	%	No./Total No.	%	No./Total No.	%
KRAS mutation	30/76	37	26/73	31	56/149	38
Codon 12	22/30	73	22/26	85	43/56	78
Codon 13	7/30	23	3/26	11	10/56	18
Codon 61	1/30	3	1/26	4	2/56	4
BRAF mutation	0/78	0	3/77	4	3/157	2
PIK3CA mutation	7/60	12	3/53	6	10/113	9
Exon 9	3/7	43	2/3	67	5/10	50
Exon 20	4/7	57	1/3	33	5/10	50
NRAS mutation	3/76	4	1/73	1	4/140	3
PTEN loss	14/72	19	5/68	7	19/130	15
Increased *EGFR* gene copy	9/65	14	4/54	7	14/119	12
Amplification	1/9	11	1/4	25	2/13	14
Polysomy	8/9	89	3/4	75	12/14	86

Abbreviations: CAPOX, capecitabine/oxaliplatin; CAPOX+C, capecitabine/oxaliplatin plus cetuximab.

Ninety five percent and 93% of patients randomly assigned to CAPOX+C and CAPOX, respectively, completed neoadjuvant chemotherapy, and 91% and 90%, respectively, completed CRT. Median treatment delays during CRT were 4 days (range, 1 to 15 days) in the CAPOX+C arm and 3 days (range, 1 to 12 days) in the CAPOX arm.

In wild-type patients, the addition of cetuximab resulted in a significant improvement in RR after neoadjuvant chemotherapy (CAPOX+C, 32 [71%] of 46 patients *v* CAPOX, 22 [51%] of 44 patients; $P = .038$; OR, 0.39; 95% CI, 0.16 to 0.96). This significant improvement was maintained after CRT (CAPOX+C, 41 [93%] of 46 patients *v* CAPOX, 32 [75%] of 44 patients; $P = .028$; OR, 0.27; 95% CI, 0.07 to 1.07; Table 3).

After CRT, 45 (98%) of 46 patients on CAPOX+C and 41 (93%) of 44 patients on CAPOX proceeded to surgery. R0 resection rates were 96% on CAPOX+C (43 of 45 patients) and 90% on CAPOX (37 of 41 patients), and there was no statistical difference between the two arms with respect to R0 resection rate, sphincter-sparing surgery rate, or surgical complication rates (Table 4). There were two perioperative deaths in the CAPOX arm. The CR and pCR rates were similar in both arms (CR: CAPOX+C, five [11%] of 46 patients *v* CAPOX, four [9%] of 44 patients; $P = 1.0$; pCR: CAPOX+C, five [11%] of 46 patients *v* CAPOX, three [7%] of 44 patients; $P = .714$).

There was no significant difference in PFS in the wild-type population (hazard ratio [HR], 0.65; 95% CI, 0.3 to 2.16; $P = .363$) between the two treatments (Fig 2). However, the addition of cetuximab resulted in a significant OS benefit (HR, 0.27; 95% CI, 0.07 to 0.99; $P = .034$; Fig 3). Relapse rates were similar in both arms, and to date, one patient in the CAPOX+C arm and two patients in the CAPOX arm have experienced local progression or local relapse. In the wild-type population, there have been three deaths

Table 4. Surgical Outcomes in All Treated Patients

	CAPOX				CAPOX+C			
	All Treated Patients (n = 81)		Wild-Type Patients (n = 44)		All Treated Patients (n = 83)		Wild-Type Patients (n = 46)	
Outcome	No.	%	No.	%	No.	%	No.	%
Underwent surgery	74	91	41	93	78	94	45	98
Operable	72	88	40	91	77	93	45	98
R0 resection	66	92	37	92	74	96	43	96
R1 resection	4	6	3	7	1	1	0	0
R2 resection	2	2	1	2	2	2	2	4
APR	22	27	11	25	23	27	13	28
Perioperative death	2	2	1	2	0	0	0	0

Abbreviations: APR, abdomino-perineal resection; CAPOX, capecitabine/oxaliplatin; CAPOX+C, capecitabine/oxaliplatin plus cetuximab.

in the CAPOX+C group from metastatic disease and nine deaths in the CAPOX arm (six deaths from metastatic disease and three non-cancer deaths). In the whole treated population, there were 19 deaths in the CAPOX arm and 12 deaths in the CAPOX+C arm; there was no difference in the rate of deaths from metastatic disease in each arm (n = 10).

Analysis of the whole treated population revealed no significant improvement in any of the end points. The HR for OS was 0.53 (95% CI, 0.26 to 1.10; $P = .083$; Fig 3). The HR for PFS was 0.81 (95% CI, 0.45 to 1.44; Fig 2). CR and pCR rates in the CAPOX+C and CAPOX arms were 18% and 14% ($P = .574$), respectively, and 18% and 15% ($P = .453$), respectively.

Table 5 lists the treatment-related grade 3 to 5 toxicities. Skin toxicity was increased during the neoadjuvant chemotherapy and CRT with cetuximab, and diarrhea was increased during the CRT only.

In univariate analysis of the whole treated patient population, the Dworak grade, MRI tumor regression grade, N stage, and the presence of extramural spread all predicted for PFS and OS. However, in multivariate analysis, only Dworak grade remained significant ($P = .018$). The significance was maintained when *KRAS* status was included in the model ($P = .005$).

The translational results are listed in Table 2. In 61 (41%) of 149 patients, paired biopsy and resection specimens were available, with 94% concordance in *KRAS/BRAF* demonstrated. On logistic regression analysis, none of the biomarkers tested predicted for CR. Both *KRAS* and PTEN loss predicted for OS on univariate analysis, but only *KRAS* remained significant for PFS and OS on multivariate analysis (OS: HR, 2.69; 95% CI, 1.192 to 5.707; $P = .016$).

DISCUSSION

Our findings demonstrate that in this group of patients with MRI-defined poor prognosis rectal cancer, neoadjuvant chemotherapy results in a high probability of disease regression, low local recurrence rates, and few deaths from metastatic disease. In contrast to the COIN (Continuous or Intermittent) and NORDIC VII data,[36,37] addition of cetuximab in *KRAS/BRAF* wild-type patients significantly improved

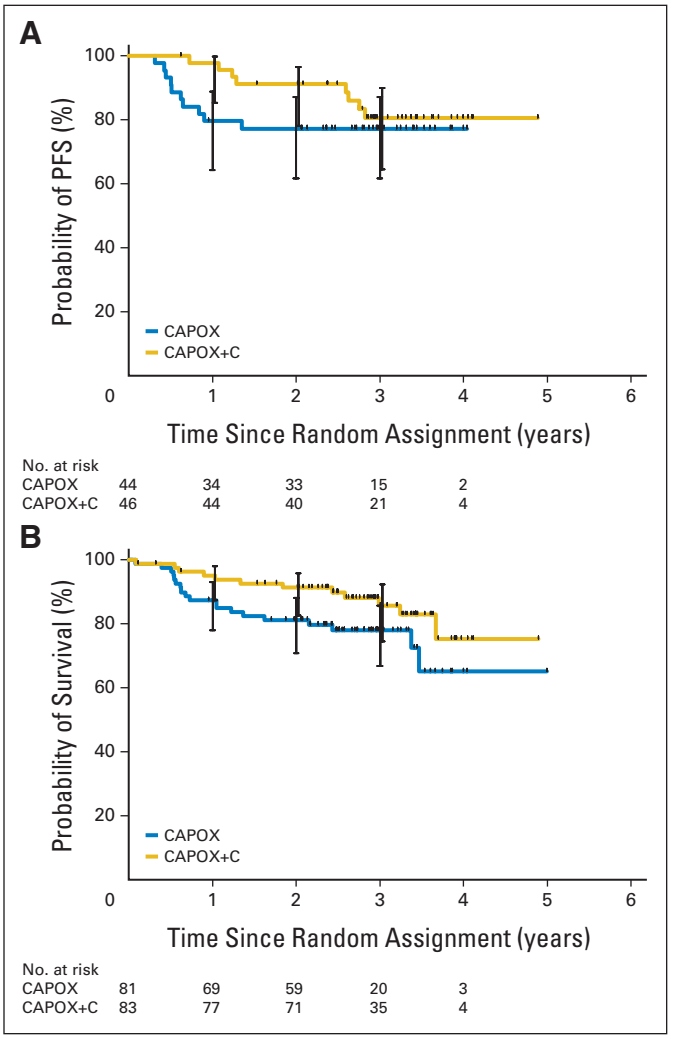

Fig 2. Kaplan-Meier analysis of progression-free survival (PFS) in (A) wild-type patients and (B) all treated patients. CAPOX, capecitabine/oxaliplatin; CAPOX+C, capecitabine/oxaliplatin plus cetuximab.

RR rates and OS, without undue toxicity. In the absence of a significant difference in PFS, the statistical improvement in survival with cetuximab is unexpected, but it is notable that in the wild-type control arm, there were six deaths from metastatic disease compared with only three in the cetuximab group. Wild-type patients in the control arm seem to experience progression earlier than patients in the cetuximab group, although the overall number of events was low. Moreover, we were encouraged by the high OS demonstrated in both arms of the study, with more than 85% of all patients alive at the time of reporting.

There was no improvement in the primary end point of CR in the wild-type population with the addition of cetuximab, and the pCR rates in both arms were lower than expected compared with data from the EXPERT trial, although consistent with contemporaneous pCR rates.[26,38] The pCR rate was potentially affected by the eight patients who achieved a pCR, six of whom were treated with cetuximab, but were not included in the analysis of the primary end point because there was insufficient tissue for molecular analysis. We recognize the ongoing debate regarding the validity of pCR as a surrogate end point in rectal cancer trials. The stage, bulk, and inherent sensitivity of the

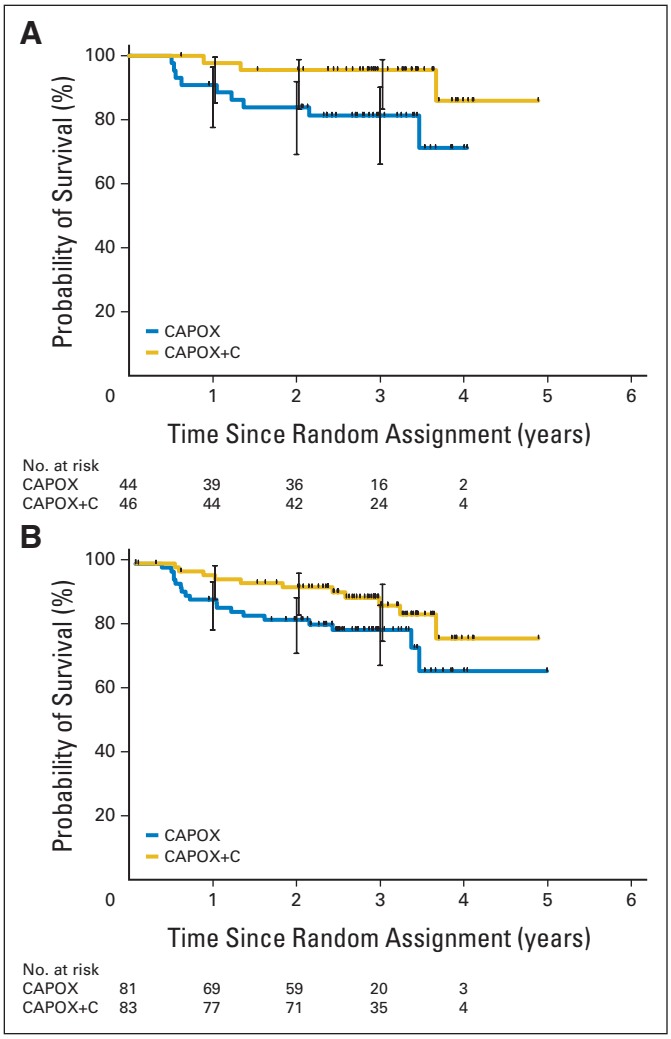

Fig 3. Kaplan-Meier analysis of overall survival in (A) wild-type patients and (B) all treated patients. CAPOX, capecitabine/oxaliplatin; CAPOX+C, capecitabine/oxaliplatin plus cetuximab.

Table 5. Treatment-Related Grade 3 to 5 Toxicity

Toxicity*	CAPOX (n = 81) No. of Patients	CAPOX (n = 81) %	CAPOX+C (n = 83) No. of Patients	CAPOX+C (n = 83) %
During neoadjuvant chemotherapy	81		83	
Febrile neutropenia	1	1	1	1
Diarrhea	7	9	7	8
Lethargy	8	10	7	10
Nausea and vomiting	2	2	2	2
Hand-foot syndrome	1	1	3	4
Stomatitis	0	0	1	1
Neuropathy	0	0	2	2
Rash	0	0	8	10
During chemoradiotherapy	75		78	
Diarrhea	1	1	8	10
Rash	0	0	7	9
Hand-foot syndrome	1	1	3	4
During adjuvant chemotherapy	52		65	
Febrile neutropenia	0	0	0	0
Diarrhea	3	6	10	16
Lethargy	1	2	7	12
Nausea and vomiting	0	0	1	2
Hand-foot syndrome	0	0	2	3
Stomatitis	0	0	1	2
Neuropathy	5	10	3	5
Rash	1	2	6	10

Abbreviations: CAPOX, capecitabine/oxaliplatin; CAPOX+C, capecitabine/oxaliplatin plus cetuximab.
*Acute toxicity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0).

tumor; the time interval between treatment and surgery; and the robustness of the pathologic analysis performed all impact on pCR. More recent studies using pCR as a primary end point demonstrate lower rates than historical controls, in keeping with an improvement in the accuracy of histologic analysis.

Our translational results are consistent with the literature and support the view that *KRAS* mutation status predicts for worse PFS and OS.[39] Importantly, there was no significant detriment to patients with *KRAS* mutations treated with CAPOX+C, contrary to data from the Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer (OPUS) and Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) studies, demonstrating inferior outcomes in patients with *KRAS* mutations treated with an anti-EGFR antibody.[40,41] It is known that distal tumors have lower *BRAF* mutation rates, and accordingly, the incidence in this study was 2%; its presence was neither prognostic nor predictive, but the numbers are too small to make a conclusion. None of the other biomarkers tested predicted for outcome, although this may be related to the modest sample size.

In this study, MRI was used to define high risk and identify patients most likely to benefit from a preoperative treatment. Nodal status is an independent predictor of systemic recurrence, and using traditional staging, the majority of patients randomly assigned had stage III disease (CAPOX 83% *v* CAPOX+C 88%). There is well-recognized heterogeneity within stage III disease, which may be subdivided into three subgroups (A, B, and C), depending on the degree of nodal involvement and mural penetration, with corresponding 3-year OS rates of 92%, 65%, and 47%, respectively.[42] The stage grouping in this study for patients treated with CAPOX+C and CAPOX was 3% and 0% for stage IIIA, 41% and 28% for stage IIIB, and 56% and 73% for stage IIIC, respectively, demonstrating that these patients were at high risk of both local and systemic recurrence. Although the presence of low tumor itself does not represent a high-risk feature, the majority of these patients had at least one additional high-risk feature. These factors suggest that patient selection alone is unlikely to account for the high OS in this study.

The completion rates of adjuvant chemotherapy in rectal cancer are often low, largely because of the toxic effects of full-dose chemotherapy in combination with toxicity from preoperative CRT plus surgery. This was demonstrated in the Grupo Cancer de Recto 3 (GCR-3) trial,[43] where 91% of patients completed induction chemotherapy but only 54% successfully completed adjuvant chemotherapy ($P < .001$). Neoadjuvant chemotherapy allows higher rates of systemic chemotherapy delivery, as demonstrated in our study. Compliance with

neoadjuvant chemotherapy in EXPERT-C was 94%, which is similar to the GCR-3 trial, but there was a higher completion rate (65%) for adjuvant chemotherapy in our study.

Skin toxicity was increased with the addition of cetuximab during chemotherapy and CRT but did not result in significant dose reductions or delays in treatment. The rate of grade 3 or 4 diarrhea (10%) was increased with cetuximab during CRT; however, the incidence was lower than the pooled 15% rate (range, 5% to 30%) reported in studies of cetuximab-based CRT.[26] Our results again contrast with the COIN trial, which demonstrated grade 3 or 4 diarrhea in 30% of patients receiving systemic therapy with cetuximab plus CAPOX (capecitabine 2,000 mg/m^2) and 16% of patients receiving capecitabine 1,700 mg/m^2. Only 8% of patients receiving systemic CAPOX+C in this study developed grade 3 or 4 diarrhea. This may be a result of the earlier stage of disease in the patients in our trial potentially reflecting better organ function compared with the metastatic setting or the lower starting dose in patients older than age 75.

This trial confirmed the efficacy of neoadjuvant systemic chemotherapy in the treatment of high-risk localized rectal cancer, and this approach warrants further investigation in patients who would otherwise receive chemotherapy as a component of their postoperative treatment. Our results demonstrate that neoadjuvant chemotherapy was well tolerated, allowed high delivery rates of systemic chemotherapy, and resulted in better than expected long-term outcomes, suggesting a possible benefit from systemic treatment before local therapy in patients with high-risk rectal cancer. However, despite an improvement in the secondary end points of RR and OS in patients with *KRAS/BRAF* wild-type rectal cancer, the primary end point of improved CR was not met, and we do not currently recommend the routine use of cetuximab in this patient population. On the basis of these results, there are sufficient data to indicate that cetuximab has some biologic activity in this setting, and further evaluation in combination with alternative chemotherapy backbones may yield more promising results.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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