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Pre- and Postoperative Capecitabine Without With Oxaliplatin in Locally Advanced Rectal Cancer: PETACC 6 Trial by EORTC GITCG and ROG, AIO, AGITG, BGDO, and FFCD

Hans-Joachim Schmoll, MD, PhD[1]; Alexander Stein, MD[2]; Eric Van Cutsem, MD, PhD[3]; Timothy Price, MBBS, DHlthSc[4]; Ralf D. Hofheinz, MD[5]; Bernard Nordlinger, MD[6]; Jean-François Daisne, MD[7]; Jos Janssens, MD[8]; Baruch Brenner, MD[9,10]; Hans Reinel, MD[11]; Stephan Hollerbach, MD[12]; Karel Caca, MD, PhD[13]; Florian Fauth, MD[14]; Carla V. Hannig, MD[15]; John Zalcberg, MBBS, PhD[16]; Niall Tebbutt, BM, BCh, PhD[17]; Murielle E. Mauer, PhD[18]; Sandrine Marreaud, MD[18]; Manfred P. Lutz, MD[19]; and Karin Haustermans, MD[3]

abstract

PURPOSE The PETACC 6 trial investigates whether the addition of oxaliplatin to preoperative capecitabine-based chemoradiation and postoperative capecitabine improves disease-free survival (DFS) in locally advanced rectal cancer.

METHODS Between November 2008 and September 2011, patients with rectal adenocarcinoma within 12 cm from the anal verge, T3/4 and/or node positive, were randomly assigned to 5 weeks preoperative capecitabine-based chemoradiation (45-50.4 Gy) followed by six cycles of adjuvant capecitabine, both without (control arm, 1) or with (experimental arm, 2) oxaliplatin. The primary end point was improvement of 3-year DFS by oxaliplatin from 65% to 72% (hazard ratio [HR], 0.763).

RESULTS A total of 1,094 patients were randomly assigned (intention to treat), and 1,068 eligible patients started their allocated treatment (arm 1, 543; arm 2, 525), with completion of protocol treatment in 68% (arm 1) *v* 54% (arm 2). A higher rate of grade 3/4 adverse events was reported in the experimental arm (14.4% *v* 37.3% and 23.4% *v* 46.6% for neoadjuvant and adjuvant treatment, respectively). At a median follow-up of 68 months (interquartile range, 58-74 months), 157 and 156 DFS events were observed in arms 1 and 2, respectively (adjusted HR, 1.02; 95% CI, 0.82 to 1.28; $P = .835$). Three-year DFS rate was not different, with 76.5% (95% CI, 72.7% to 79.9%) in arm 1, which is higher than anticipated, and 75.8% (95% CI, 71.9% to 79.3%) in arm 2. The 7-year DFS and overall survival (OS) rates were not different as well, with DFS of 66.1% *v* 65.5% (HR, 1.02) and OS of 73.5% *v* 73.7% (HR, 1.19) in arms 1 and 2, respectively. Subgroup analyses revealed heterogeneity in treatment effect according to German versus non-German site location, without detectable confounding factors in multivariable analysis.

CONCLUSION The addition of oxaliplatin to preoperative capecitabine-based chemoradiation and postoperative adjuvant chemotherapy impairs tolerability and feasibility and does not improve efficacy.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In localized rectal cancer stage II/III (cT3/4 or any lymph node involvement), neoadjuvant chemoradiation therapy (CRT) with fluoropyrimidine, followed by total mesorectal excision (TME) and adjuvant fluoropyrimidine-based chemotherapy, has become a standard of care.[1-3] To improve local control and distant failure, the PETACC 6 trial, alongside several other trials, was launched to assess the impact of the addition of oxaliplatin to neoadjuvant CRT and in parallel with CAO/ARO/AIO-04 to adjuvant chemotherapy.[4-7] PETACC 6 was initiated in 2008 to compare neoadjuvant CRT with concurrent capecitabine, followed by TME and adjuvant capecitabine, with neoadjuvant CRT with capecitabine and oxaliplatin (CAPOX), followed by TME and adjuvant CAPOX. The chemotherapy chosen was based on prior data showing the feasibility of CRT with capecitabine with or without oxaliplatin and the proven similar efficacy of fluorouracil (5FU) and capecitabine as single agent in adjuvant colon cancer.[8-15]

METHODS

Patients

Eligible patients were age ≥ 18 years with pathologically confirmed rectal cancer, inferior margin up to

CONTEXT

Key Objective

To define the impact of adding oxaliplatin to perioperative capecitabine-based neoadjuvant chemoradiation therapy and adjuvant chemotherapy in locally advanced rectal cancer.

Knowledge Generated

The addition of oxaliplatin to perioperative multimodality treatment impairs feasibility and tolerability and does not improve short-term (pathologic response) or long-term outcome (survival).

Relevance

There is no role for oxaliplatin in neoadjuvant capecitabine-based chemoradiation therapy and postoperative adjuvant chemotherapy.

12 cm from the anal verge (by rigid proctoscopy), and clinical T3/4 or any T with lymph node involvement (cN+; by endorectal ultrasound [EUS] and/or pelvic magnetic resonance imaging [MRI] or, if MRI not available, computed tomography [CT] plus EUS). Pretreatment CT scan of the chest and abdomen was required to exclude metastatic disease. Additional inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2 and adequate hematologic, liver, and renal function. Exclusion criteria were metastatic disease, prior pelvic radiotherapy (RT) or chemotherapy, other cancers within the past 5 years, pregnancy, lactation, clinically significant cardiac disease, and known peripheral neuropathy.

Random Assignment

Patients were centrally (European Organisation for Research and Treatment of Cancer [EORTC] data center) randomly assigned using a 1:1 allocation ratio to the control arm with pre- and postoperative capecitabine or to the experimental arm with pre- and postoperative CAPOX. Random assignment was not blinded and stratified for institution, clinical T category (T1-3 *v* T4), clinical nodal status (NX *v* N0 *v* N1-2), distance from the tumor to the anal verge ($\leq$ 5 cm *v* $>$ 5 cm), and locoregional staging method (EUS + MRI *v* EUS + CT *v* MRI alone).

Procedure

In the control arm, neoadjuvant CRT with 45 or 50.4 Gy with concurrent capecitabine 2 $\times$ 825 mg/m^2 twice daily without weekends, followed by TME and adjuvant capecitabine with 1,000 mg/m^2 twice daily on days 1-15 every 3 weeks for six cycles was applied. In the experimental (CAPOX) arm, oxaliplatin was added to the same capecitabine dose during neoadjuvant CRT with 50 mg/m^2 for days 1, 8, 15, 22, and 29 and during adjuvant chemotherapy with 130 mg/m^2 on day 1 every 3 weeks for six cycles (Data Supplement, online only).

RT consisted of 45 Gy in 25 fractions (1.8 Gy daily, Monday-Friday), delivered with a minimum energy of 6-MV photons through a three-field or four-field box technique to the primary tumor and to mesorectal, presacral, and internal iliac lymph nodes. An additional dose of 5.4 Gy could be given using the same fields or as a boost to the macroscopic tumor (primary and nodes) up to a total dose of 50.4 Gy in 28 fractions (1.8 Gy per fraction). Centers had to choose one option (45 or 50.4 Gy) and adopt it for both arms for the entire study. Surgery was planned 4-6 weeks after completion of neoadjuvant treatment. Before surgery, a clinical evaluation of response was performed using digital rectal examination; pelvic MRI; or, if MRI was not available, CT, EUS, and abdominal CT. Surgical technique was left to the surgeon, and TME was regarded as standard of care. Pathology was based on TNM classification International Union Against Cancer (UICC) sixth edition, including number of examined and involved lymph nodes and status of proximal, distal, and circumferential resection margins.

Adjuvant treatment of 4.5 months with capecitabine with or without oxaliplatin was started within 6-8 weeks postoperatively. Follow-up measures were carcinoembryonic antigen (every 3 months for years 1-3, every 6 months for years 4-5, chest CT every 12 months and abdominal CT or ultrasound every 6 months for years 1-3; for years 4-5, only EUS every 12 months). In case of no complete colonoscopy preoperatively, colonoscopy was performed 6 months and 3 years after adjuvant treatment.

Patients were monitored weekly during CRT and before each adjuvant treatment cycle for adverse events, vital signs, ECOG PS, and laboratory measurements. Dose modifications were done according to toxicity (National Cancer Institute Common Terminology Criteria for Adverse Events [version 3.0; CTCAE v3.0]). Patients were followed for overall survival (OS) for at least 5 years after the end of postoperative study treatment or death.

Statistical Analysis

The primary end point of disease-free survival (DFS) was defined from random assignment to the first event: locoregional failure, metastatic recurrence, secondary colorectal cancer, or death. R2 resection distant metastases at surgery were considered treatment failures.

The trial was planned to detect a 3-year DFS improvement from 65% to 72% (hazard ratio [HR], 0.763), with 80% power at a two-sided 5% significance level on the basis of an interim analysis for early efficacy at year 3 after the start of the recruitment or at 200 events. Accounting for that interim analysis, the final analysis was to be conducted with a one-sided α of 0.023 on the basis of 440 events. Assuming 2.8 years of recruitment and 3 additional years of follow-up, a total of 1,090 patients were to be randomly assigned to observe the required 440 events.

Secondary end points were OS, locoregional or distant failure, pathologic downstaging (ypT0-2N0) rate, pathologic complete remission (pCR; ypT0N0) rate, tumor regression grade, histopathologic R0 resection rate, sphincter

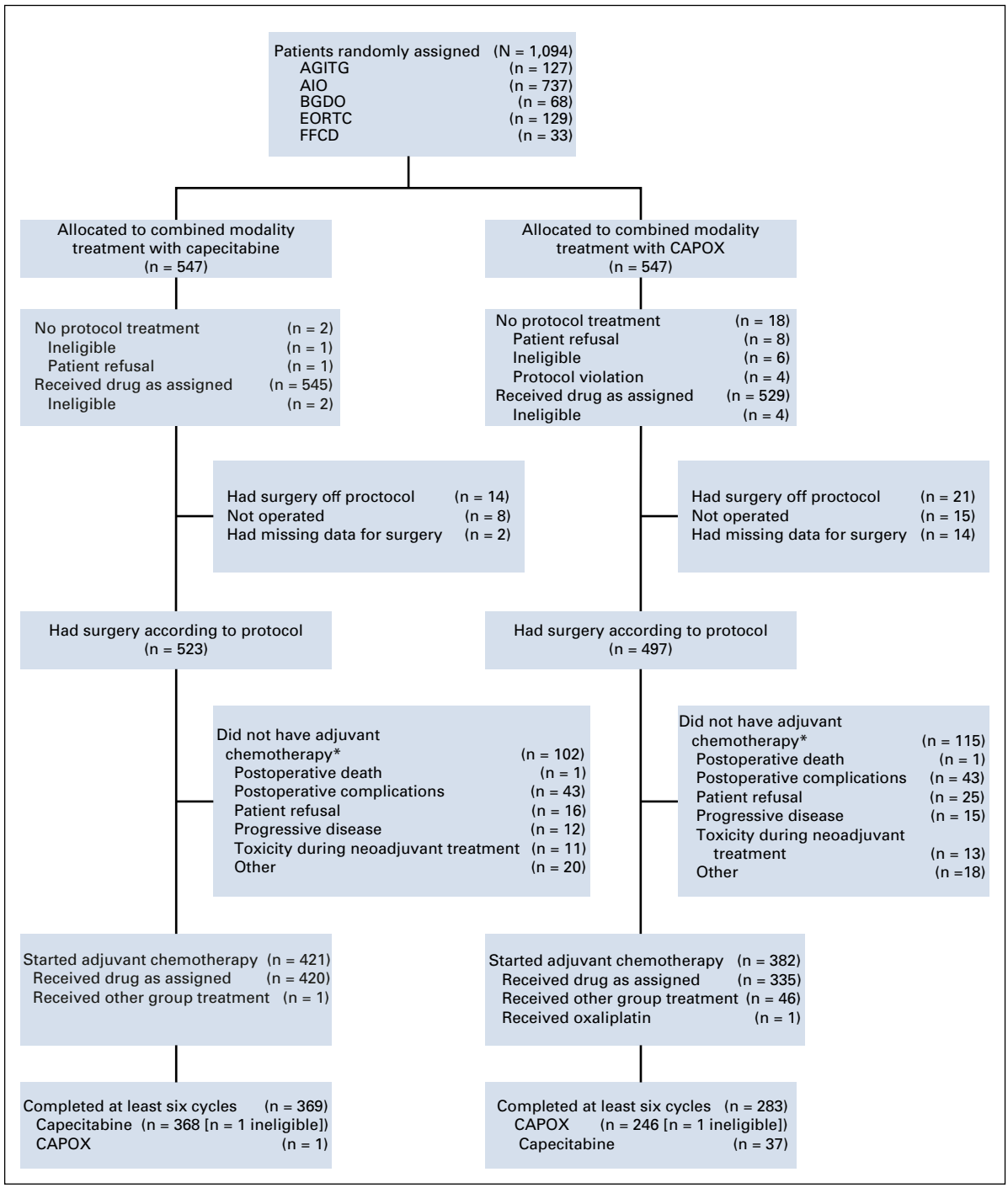

FIG 1. CONSORT diagram. AGITG, Australasian Gastro-Intestinal Trials Group; AIO, Arbeitsgemeinschaft Internistische Onkologie; BGDO, Belgian Group of Digestive Oncology; CAPOX, capecitabine and oxaliplatin; EORTC, European Organisation for the Research and Treatment of Cancer; FFCD, Fédération Francophone de Cancérologie Digestive.

TABLE 1. Baseline Characteristics

Characteristic	Cape + RT, No. (%)	CAPOX + RT, No. (%)
No. of patients	547	547
Median age, years (range)	62 (26-87)	62 (23-82)
Sex		
Male	394 (72.0)	380 (69.5)
Female	153 (28.0)	167 (30.5)
ECOG PS		
0	420 (76.8)	432 (79.0)
1	126 (23.0)	108 (19.7)
2	1 (0.2)	7 (1.3)
cT		
cT1	3 (0.5)	2 (0.4)
cT2	36 (6.6)	33 (6.0)
cT3	466 (85.2)	469 (85.7)
cT4	42 (7.7)	43 (7.9)
cN		
cN0	118 (21.6)	120 (21.9)
cN1	295 (53.9)	296 (54.1)
cN2	98 (17.9)	93 (17.0)
cNX	36 (6.6)	38 (6.9)
TNM stage		
II	116 (21.2)	120 (21.9)
III	392 (71.7)	386 (70.6)
cT3-4, cNX	35 (6.4)	38 (6.9)
Missing	4 (0.7)	3 (0.5)
Distance of tumor to anal verge, cm		
≤ 5	236 (43.1)	237 (43.3)
> 5	311 (56.9)	310 (56.7)
MRI available at the center		
No	66 (12.1)	56 (10.2)
Yes	481 (87.9)	491 (89.8)
Locoregional staging performed by		
EUS + MRI	229 (41.9)	224 (41.0)
EUS + CT scan	192 (35.1)	207 (37.8)
MRI alone	126 (23.0)	116 (21.2)

Abbreviations: Cape, capecitabine; CAPOX, capecitabine and oxaliplatin; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EUS, endorectal ultrasound; MRI, magnetic resonance imaging; RT, radiotherapy.

preservation rate, perioperative complication rate, and toxicity according to CTCAE v3.0 (refer to the Appendix, online only, for specifications of statistical analyses).

Because of the higher toxicity in the experimental arm, the safety data were reviewed (unplanned review) by the EORTC independent data monitoring committee (IDMC) in May 2011, which recommended continuation of the trial given that the targeted DFS benefit was judged to still represent a positive risk:benefit ratio. However, the events had not accumulated at the pace expected, given that the 3-year DFS was higher in the control arm than anticipated. The interim analysis was performed in May 2013 at 225 events. The EORTC IDMC recommended the early release of the data on basis of futility while continuing follow-up until the planned final analysis.

RESULTS

From November 2008 to September 2011, 1,094 patients (n = 547 in each arm) were randomly assigned in 181 centers in Australia, Belgium, France, Germany, Israel, and

TABLE 2. Treatment Exposure During Neoadjuvant CRT and Adjuvant Chemotherapy

Treatment	Neoadjuvant CRT, No. (%)				Adjuvant Chemotherapy, No. (%)	
	Capecitabine + RT (n = 545[a])		CAPOX + RT (n = 532[a])		Capecitabine + RT (n = 420)	CAPOX + RT (n = 335)
Planned RT, Gy						
45	109 (20.0)		113 (21.2)			
50.4 (same fields)	156 (28.6)		141 (26.5)			
50.4 (boost)	276 (50.6)		275 (51.7)			
50.4 (unknown)	4 (0.7)		3 (0.6)			
Received planned dose	534 (98.0)		499 (93.8)			
RT not started	0 (0.0)		1 (0.2)[b]			
RT prematurely stopped						
Toxicity	8 (1.5)		19 (3.6)			
Temporary interruption						
Toxicity	22 (4.0)		67 (12.6)			
Capecitabine					421c	381c
Relative dose intensity (%)	45 Gy (n = 222)	50.4 Gy (n = 855)	45 Gy (n = 222)	50.4 Gy (n = 855)		
Median	92.1	97.8	90.8	95.1	94.1	89.1
Range	52.8-115.3	53.1-140.0	26.7-28.6	28.4-145.8	30.5-124.5	10.5-112.3
Any toxicity-related dose reduction or withdrawal	57 (10.5)		165 (31.0)		101 (24.0)	142 (37.3)
Non-hematological toxicity	52 (9.5)		151 (28.4)			
Oxaliplatin, No. of patients						336[d]
Median relative dose, % (range)			98.7 (0.0-128.0)			84.4 (11.4-300.9)
Any toxicity-related dose reduction or withdrawal			119 (22.4)			161 (47.9)
Nonhematologic toxicity			102 (19.2)			

Abbreviations: CAPOX, capecitabine and oxaliplatin; CRT, chemoradiation therapy; RT, radiotherapy.

[a]Patients who started preoperative treatment.

[b]Discontinuation because of a serious adverse event.

[c]All patients operated on within protocol who started postoperative capecitabine.

[d]All patients operated on within protocol who started postoperative oxaliplatin.

New Zealand. A total of 1,068 patients were eligible (543 in the control arm and 525 in the experimental arm; Fig 1), with 12 patients ineligible, one unverifiable, four having protocol violations, and nine withdrawing consent. Baseline characteristics were well balanced between arms (Table 1). The local staging at baseline was EUS and MRI in 453 patients (41.4%), EUS and pelvic CT scan in 399 (36.5%), and MRI alone in 242 (22.1%).

Neoadjuvant CRT

RT dose (45 *v* 50.4 Gy) was balanced between the treatment arms, with 20% of patients receiving 45 Gy. Completion rates of planned RT were 98% and 94% (Table 2). Treatment compliance during neoadjuvant CRT was as expected and well balanced, with the exception of dose modifications for capecitabine (31% in the experimental arm *v* 10.5% in the control arm) mainly because of nonhematologic toxicity (Table 2). Accordingly, dose modifications for oxaliplatin in the experimental arm (22.4%) were correlated to capecitabine modifications ($P < .0001$). Of note, surgical and pathologic outcomes were not influenced by dose modifications (Appendix Table A1, online only). Furthermore, the rate of grade 3/4 diarrhea was approximately tripled by the addition of oxaliplatin to capecitabine-based RT (Table 3).

Surgery

Type of surgery as well as postoperative morbidity and mortality did not relevantly differ between arms, with TME in 89% of both, any postoperative complications (41.9% *v*

TABLE 3. Toxicity During Neoadjuvant CRT and Postoperative Chemotherapy

	Neoadjuvant CRT, No. (%)		Adjuvant Chemotherapy, No. (%)	
Toxicity (NCI CTCAE v3.0)	**Capecitabine + RT**	**CAPOX + RT**	**Capecitabine**	**CAPOX**
No. of patients	545[a]	529[a]	420[b]	335[b]
All grade 3-4	79 (14.5)	197 (37.2)	99 (23.6)	155 (46.3)
Grade 3-4 GI	43 (7.9)	115 (21.7)	32 (7.6)	76 (22.6)
Diarrhea	33 (6.1)	98 (18.5)	23 (5.4)	42 (12.5)
Nausea	3 (0.6)	13 (2.5)	2 (0.5)	17 (5.1)
Vomiting	3 (0.6)	9 (1.7)	1 (0.2)	18 (5.4)
Stomatitis	1 (0.2)	3 (0.6)	2 (0.5)	2 (0.6)
Proctitis	7 (1.3)	9 (1.7)	NA	NA
Grade 3-4 general				
Infection	7 (1.3)	14 (2.7)	9 (2.3)	14 (4.2)
Fatigue	2 (0.4)	20 (3.8)	6 (1.4)	16 (4.8)
Grade 3-4 renal/genitourinary	1 (0.2)	10 (1.9)	10 (2.4)	6 (1.8)
Grade 3-4 radiation dermatitis	8 (1.5)	9 (1.7)	NA	NA
Grade 3-4 hand-foot syndrome	0 (0)	1 (0.2)	22 (5.2)	7 (2.1)
Grade 2-4 neuropathy	1 (0.2)	48 (9.1)	12 (2.9)	113 (33.7)

Abbreviations: CAPOX, capecitabine and oxaliplatin; CRT, chemoradiation therapy; NA, not applicable; NCI CTCAE v3.0, National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0); RT, radiotherapy.

[a]All patients who started their allocated treatment.

[b]All patients operated on within protocol and who started the allocated postoperative treatment.

45.9% in the control *v* experimental arms, respectively), and mortality in three patients per arm (Table 4). In the intention-to-treat population with data available, the composite end point perioperative complication rate (defined as prolongation of hospitalization > 20 days after surgery) or a severe event within 30 days of surgery (new hospitalization, re-operation, or death as a result of severe surgery-related complication; organ failure; severe bleeding; thromboembolism; major impaired wound healing delaying start of adjuvant chemotherapy by > 8 weeks; or severe pre- or postoperative treatment-related toxicity inducing a > 8-week delay of surgery or treatment discontinuation or death) was significantly lower in the control arm (30.6%) than in the experimental arm (40.3%; $P = .0009$; Table 4).

Adjuvant Chemotherapy

In the control arm, 77% (n = 420) started adjuvant capecitabine (with one patient receiving CAPOX) compared to only 61% (n = 335) in the experimental arm starting on adjuvant CAPOX as planned and further 8% (n = 46) on capecitabine only and one patient on oxaliplatin only. Furthermore, of those who started adjuvant chemotherapy, significantly fewer patients in the experimental arm completed the planned duration of 4.5 months (74% *v* 88%; $P < .0001$). Post hoc analysis showed better outcomes in patients starting adjuvant chemotherapy compared with patients without adjuvant chemotherapy after surgery (Appendix Table A2, online only). Toxicity was as expected, with a higher rate of GI adverse events and neuropathy in the experimental arm compared with capecitabine alone (Table 3).

Primary and Secondary End Points

The rates of pathologic tumor downstaging were comparable in both arms (Table 4) (ypT0-2 N0, 44.9% *v* 44.4%; pCR [ypT0 N0], 11.6% *v* 14.0%; tumor regression grade [Dvorak 2-4], 70.9% *v* 75.8%; and sphincter preservation rate, 71.3% *v* 69.9% in the control *v* experimental arms, respectively). The pathologic R0 resection rate with 93.4% (control) *v* 95.8% (experimental) was not different ($P = .084$; Table 4).

The cumulative incidence of locoregional and distant failure at 5 years were similar in both arms. The 5-year locoregional failure rate was 8.68% (95% CI, 6.22% to 11.14%) in the control arm *v* 6.02% (95% CI, 3.93% to 8.11%) in the experimental arm ($P = .204$; Fig 2A). The 5-year distant failure rate was 21.43% (95% CI, 17.88% to 24.97%) in the control arm *v* 19.22% (95% CI, 15.77% to 22.67%) in the experimental arm ($P = .246$; Fig 2B).

Overall, 157 and 156 DFS events were observed in the control and experimental arms, respectively. The 3-year DFS rate was similar with 76.5% (95% CI, 72.7% to 79.9%) in the control arm and, thus, higher than the anticipated 65%, *v* 75.8% (95% CI, 71.9% to 79.3%) in the experimental arm. The addition of oxaliplatin to the perioperative treatment did not improve DFS (HR, 1.02; 95% CI, 0.82 to 1.28; $P = .835$; Fig 2C). The 5- and 7-year DFS rates were

TABLE 4. Surgical Procedures and Outcome of All Patients Operated on Within the Protocol and Surgical or Pathologic End Points Pertaining to the Surgical Outcome According to Treatment Arm (ITT)

Variable	Percentage,[a] No. (%)		OR[b] (95% CI)	P[b]
	Cape + RT	CAPOX + RT		
Surgical procedures and outcome, No. of patients operated on within the protocol	523	497		
Type of surgery				
Laparoscopy	153 (29.3)	138 (27.8)		
Laparotomy	367 (70.2)	354 (71.2)		
Unknown	3 (0.6)	5 (1.0)		
Surgical procedure				
Low anterior resection	383 (73.2)	352 (70.8)		
Abdominoperineal resection	136 (26.0)	136 (27.4)		
Other	4 (0.8)	4 (0.8)		
Missing	0 (0.0)	5 (1.0)		
Total mesorectal excision	466 (89.1)	445 (89.5)		
Postoperative morbidity				
Any complication[b] (any grade)	219 (41.9)	228 (45.9)		
Anastomotic dehiscence	35 (6.7)	35 (7.0)		
Impaired wound healing				
Minor	49 (9.4)	48 (9.7)		
Major	38 (7.3)	37 (7.4)		
Bowel obstruction	15 (2.9)	13 (2.6)		
Fistula	16 (3.1)	13 (2.6)		
Severe sepsis	6 (1.1)	10 (2.0)		
Renal failure requiring dialysis	2 (0.4)	6 (1.2)		
Second surgery for complications	55 (10.5)	54 (10.9)		
Death due to PETACC 6 surgery	3 (0.6)	3 (0.6)		
SAE during/as a result of surgery	102 (19.5)	126 (25.4)		
End points pertaining to the surgical outcome according to treatment arm (ITT), No. of patients	547	547		
Perioperative complication rate, %	30.6	40.3	1.53 (1.19 to 1.97)	.0009
Pathologic downstaging (ypT0-2N0) rate, %	44.9	44.4	0.98 (0.77 to 1.25)	.890
pCR (ypT0N0) rate, %	11.6	14.0	1.25 (0.87 to 1.79)	.225
Histopathologic R0 resection rate, %	95.8	93.4	0.62 (0.36 to 1.07)	.084
Tumor regression grade (Dworak)			1.28 (0.97 to 1.69)	.077
No/minimal regression (0, 1)	29.1	24.2		
Moderate/good/total regression (2-4)	70.9	75.8		
Sphincter preservation rate	71.3	69.9	0.96 (0.71 to 1.29)	.781

Abbreviations: Cape, capecitabine; CAPOX, capecitabine and oxaliplatin; ITT, intention to treat; OR, odds ratio; pCR, pathologic complete remission; RT, radiotherapy; SAE, serious adverse event.

[a]Percentages are for patients with available data. Patients not operated on or not receiving a resection were considered to have experienced treatment failure in the analyses.

[b]ORs, 95% CIs, and *P* values were computed from a logistic regression model with adjustment for all stratification factors except center. Patients with missing data were removed from the analyses.

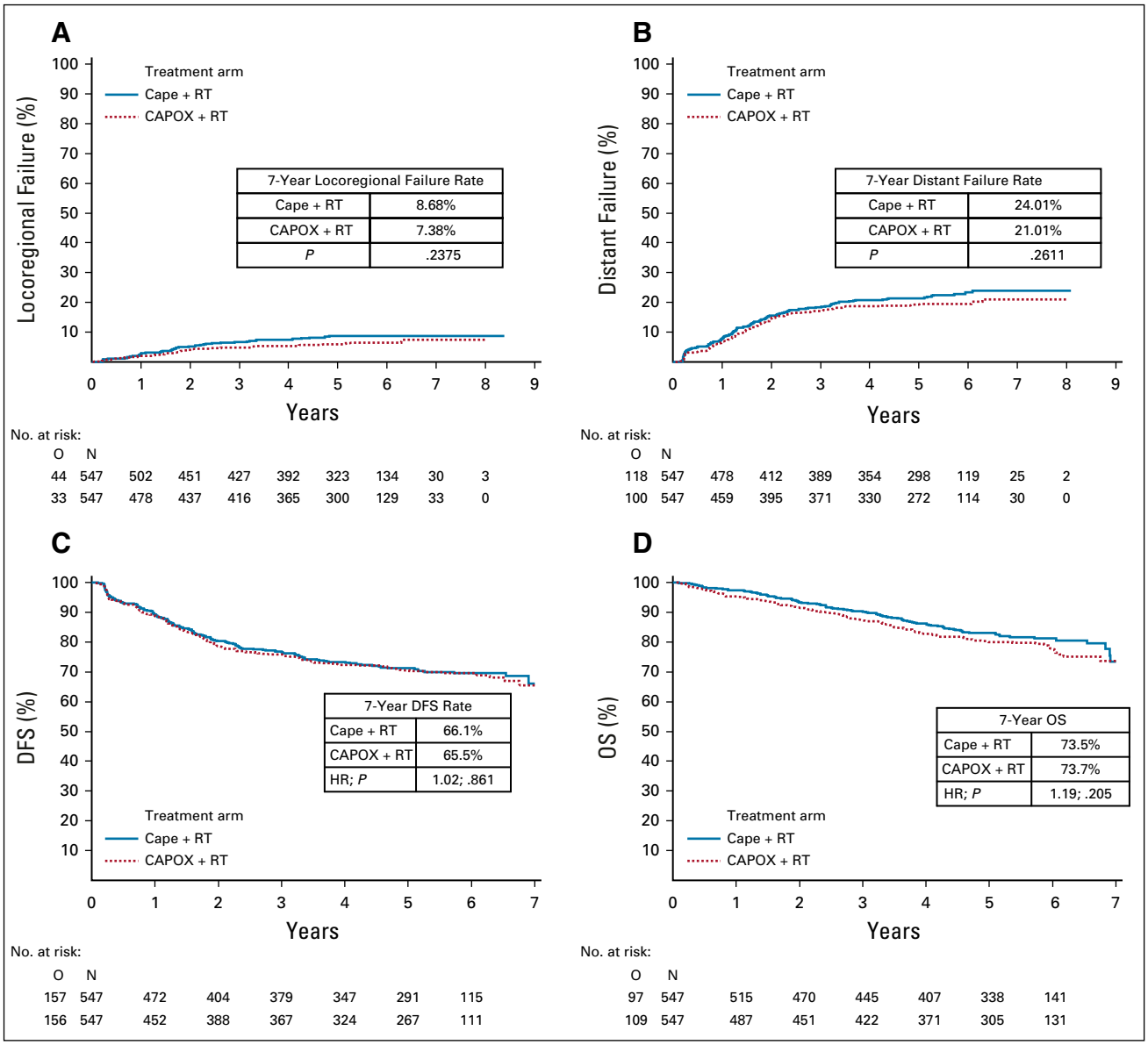

FIG 2. (A) Locoregional and (B) distant failures and (C) disease-free survival (DFS) and (D) overall survival (OS) at 7 years follow-up by treatment arm. Cape, capecitabine; CAPOX, capecitabine and oxaliplatin; HR, hazard ratio; N, number of patients at risk; O, observed events; RT, radiotherapy.

71.3% *v* 70.5% and 66.1% *v* 65.5% for the control versus experimental arms, respectively. There was no difference in 5-year OS rate (83.1% *v* 80.1%) and 7-year OS rate (73.5% *v* 73.7%) in the control versus experimental arms, respectively (HR, 1.19; 95% CI, 0.91 to 1.57; $P = .205$; Figs 2C and 2D).

Post Hoc Subgroup Analyses

Retrospective subgroup analyses did not reveal any heterogeneity in treatment effect on DFS according to major baseline factors, except for country of patient inclusion ($P = .01$; Fig 3). However, multiple tests were performed without adjusting the level of significance.

No impact of the addition of oxaliplatin was noted in stage II (21% of patients) for DFS (HR, 0.95; $P = .82$) or OS (HR, 0.95; $P = .84$) and in stage III (72%; 7% cT3-4, cNX) for DFS (HR, 1.04; $P = .78$) or OS (HR, 1.21, $P = .27$; Data Supplement).

However, strong and inverse differences were observed in patients included at German sites (n = 737): oxaliplatin with a numerically decreased DFS rate at 5 years (73.4% *v* 67.8%; HR, 1.27; $P = .092$) in contrast to non-German sites (n = 357) with a numerically increased DFS rate at 5 years (67.0% *v* 75.7%; HR, 0.70; $P = .061$; Data Supplement). Main differences were stage distribution and staging with MRI at baseline (Appendix Table A3, online only) and rates of application of adjuvant chemotherapy (Appendix Table A2).

The multivariable prognostic analysis in pooled treatment arms identified older age (> 60 years), cT3-4 disease, and

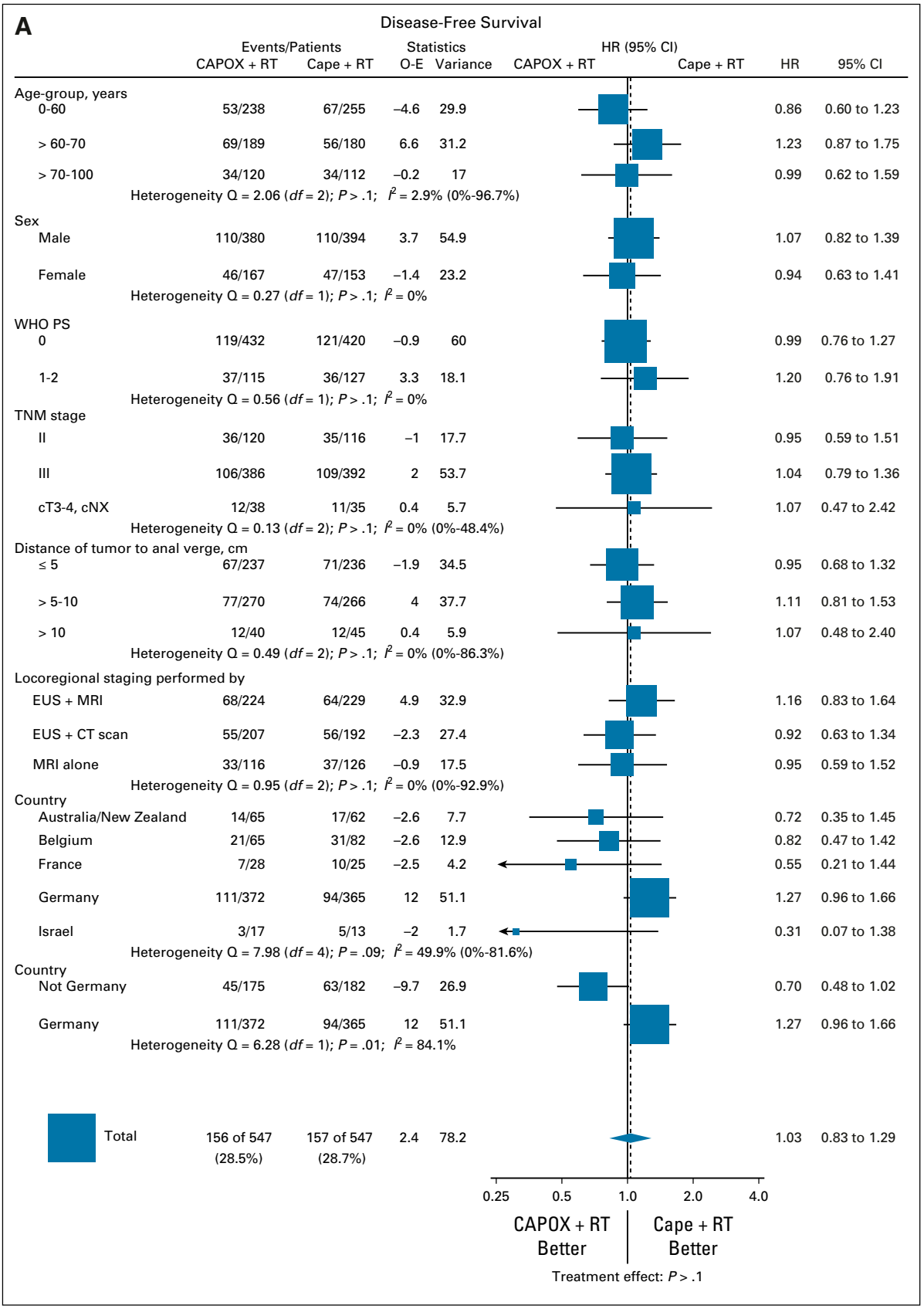

FIG 3. Forest plot of subgroup analyses for disease-free survival and overall survival according to major baseline factors. CT, computed tomography; EUS, endorectal ultrasound; HR, hazard ratio; MRI, magnetic resonance imaging; O-E, XXXX; PS, performance status.

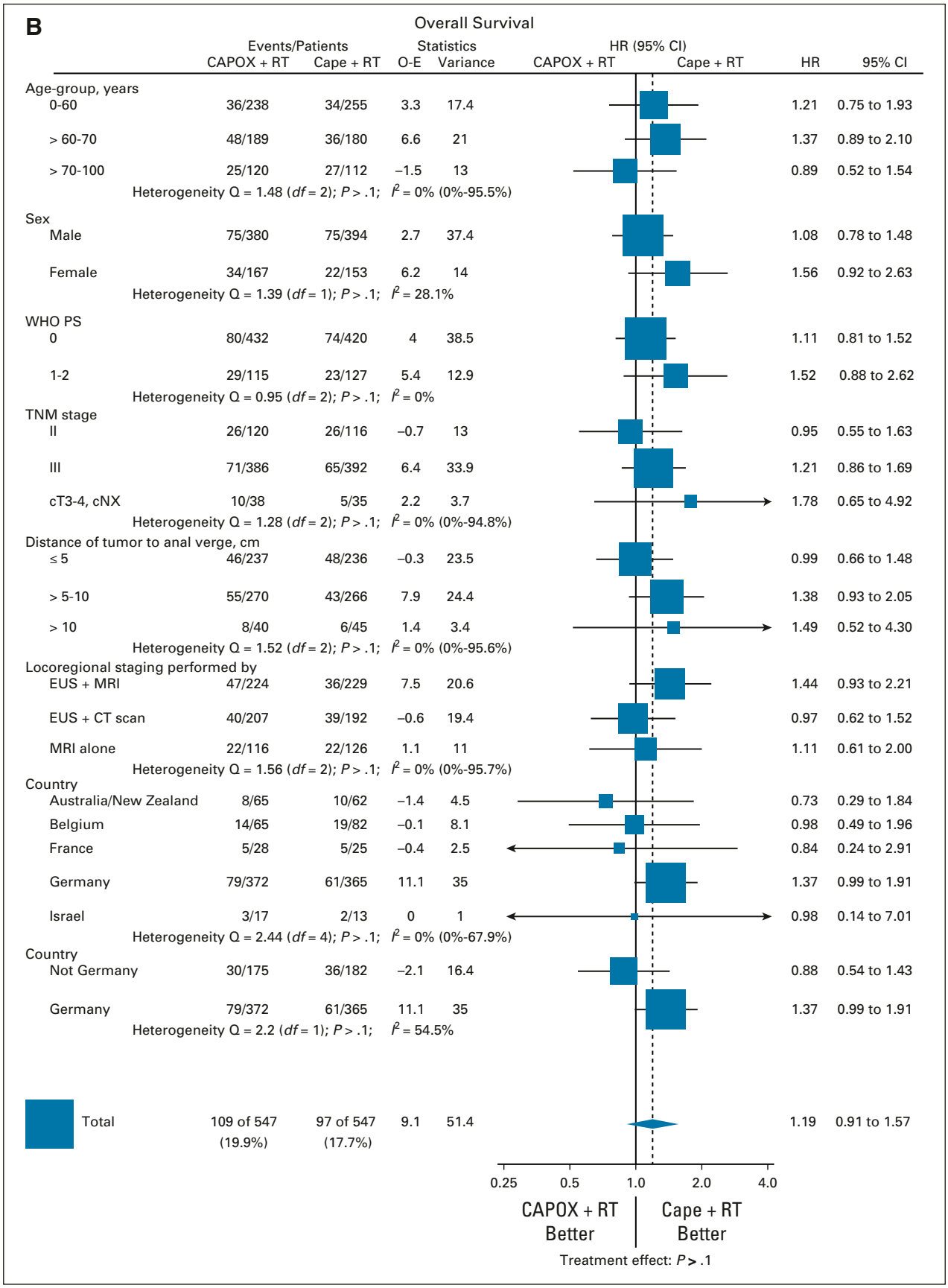

FIG 3. (Continued).

a low location (no sphincter preservation possible as judged by the surgeon) as independent prognostic factors for a worse DFS (Appendix Table A4, online only). When adding predictive factors (interactions of baseline factors with treatment arm), to be treated outside Germany was the only baseline predictive factor for treatment benefit of oxaliplatin in the multivariable model. In the multivariable analysis, the interaction of country (Germany *v* not Germany) with treatment remained statistically significant (Appendix Table A5, online only). Therefore, it was not possible to explain the possible heterogeneity in DFS results by these baseline factors.

DISCUSSION

PETACC 6 was designed to show an increase in DFS by the addition of oxaliplatin to capecitabine-based perioperative treatment. The study could not demonstrate a benefit of adding oxaliplatin to perioperative capecitabine in terms of DFS, OS, local and distant failure, or pathologic and surgical end points. Furthermore, the addition of oxaliplatin resulted in worse tolerability with a higher rate of grade 3/4 toxicities (mainly diarrhea), particularly in the neoadjuvant CRT part with a tripled rate (6.1% *v* 18.5%). In contrast to purely adjuvant trials in colon cancer, the rate of grade 3/4 diarrhea remained relevantly higher by the addition of oxaliplatin (5.4% *v* 12.5%), likely an effect of the preceding CRT.[16] Because of the increased toxicity, the capecitabine dose had to be reduced or withdrawn in nearly every third patient in the combination arm compared with 10.5% in the control arm.

Moreover, the perioperative complication rate was significantly higher in the combination group. Likely, the impaired feasibility of capecitabine in the experimental arm resulted in similar pathologic and surgical secondary end points.

Overall, the PETACC 6 results are in line with other trials that investigated the addition of oxaliplatin to preoperative CRT[4-7,17-19] (Appendix Table A6, online only). Four of these five trials showed no or only marginal benefit in terms of pCR rate or survival end points. Only the CAO/ARO/AIO-04 trial is comparable to PETACC 6, having had randomly assigned oxaliplatin not only to the neoadjuvant CRT arm but also to the adjuvant treatment arm. In contrast to PETACC 6, a modest, but significant increase in the pCR rate of 4% and DFS rate (71.2% *v* 75.9%; HR, 0.79; $P = .03$) was shown, with no impact of survival (HR, 0.96). However, compared with PETACC 6, CAO/ARO/AIO-04 applied a different fluoropyrimidine regimen in both arms comparing the CAO/ARO/AIO-94 regimen with continuous infusion 5FU 1,000 mg/m^2 on days 1-5 and 29-33 (control arm) during RT and four cycles of postoperative bolus 5FU with 500 mg/m^2 on days 1-5 every 4 weeks with continuous 5FU 250 mg/m^2 on days 1-14 and 22-35 in combination with oxaliplatin 50 mg/m^2 on days 1, 8, 22, and 29 during RT and postoperatively for eight cycles of a modified infusional 5FU, leucovorin, and oxaliplatin regimen.[1,5] Because there are two variables, the impact of oxaliplatin on the beneficial results is not fully clear. Furthermore, the STAR 1, ACCORD 12/0405-Prodige 2, NSABP R04, and PETACC 6 trials with similar fluoropyrimidine doses and schedules in both arms have not been able to show any difference by the addition of oxaliplatin to preoperative CRT and in PETACC 6, to adjuvant chemotherapy as well. On the basis of the available data comparing capecitabine with 5FU in the perioperative treatment of rectal cancer and capecitabine with bolus 5FU as well as CAPOX with bolus 5FU in the adjuvant setting of UICC stage III colon cancer, capecitabine seems to be more efficacious than 5FU in the perioperative treatment of colorectal cancer.[14,15,20] Therefore, it might be speculated that compared with the CAO/ARO/AIO-04 trial, the PETACC 6 design that applied a highly efficacious control arm with single-agent capecitabine precluded any relevant benefit by the addition of oxaliplatin.

Besides the design issues, the impaired tolerability of the combination arm clearly limited the feasibility of the perioperative treatment. In PETACC 6, only 382 patients (70% from the baseline population) in the combination arm compared with 421 patients (77%) in the control arm started adjuvant chemotherapy. Furthermore, the completion rate was lower in the combination arm (76% *v* 88%). These different rates, which are in clear contrast to the well-balanced rates in the CAO/ARO/AIO-04 trial, might also be the reason for the lack of DFS benefit in PETACC 6. However, oxaliplatin-based adjuvant chemotherapy for postoperatively selected high-risk patients with ypT3/4 or ypN+ compared with bolus 5FU and leucovorin resulted in a DFS benefit (HR, 0.63; $P = .018$), as currently shown in the randomized phase II ADORE trial.[21,22]

The post hoc subgroup analyses revealed several interesting and not fully explained results. In PETACC 6, a trend favoring CAPOX in the age-group $\leq$ 60 years, although not significant and only marginally, supports the corresponding findings of CAO/ARO/AIO-04, with significant improvement of DFS but without any effect on OS. Of note, the study site location (Germany *v* not Germany) was predictive for oxaliplatin benefit, with a crossing over of the DFS results in both arms (Data Supplement). Staging, particularly the use of MRI and the application of adjuvant chemotherapy, relevantly differed between German and non-German sites, but this does not explain the strong difference in outcome. In addition, besides the overall favorable clinical T and N stage in Germany, the control group in Germany showed a trend toward favorable clinical and pathologic T and N stage compared with the other groups. Although multivariable analysis did not identify potential factors beyond the different outcome for the country of origin, further in-depth analysis is necessary and currently planned. However, careful interpretation of these subgroup analyses is necessary because of the inherent limitations of retrospective analyses.

In conclusion, perioperative multimodality treatment with CAPOX did not improve pCR, DFS, and OS but resulted in increased toxicity and, therefore, decreased feasibility of preoperative CRT. This trial adds evidence that the addition of oxaliplatin to capecitabine-based CRT adds toxicity without a benefit, which is consistent with most prior experience. Thus, oxaliplatin-based CRT should not be applied. The toxicity of the addition of oxaliplatin to postoperative capecitabine strongly limits the optimal dose, which might have been responsible for the inefficacy of oxaliplatin in this trial. Therefore, if any, the potential of oxaliplatin as part of preoperative chemotherapy is currently being investigated for the development of the total neoadjuvant treatment strategy.[23]

AFFILIATIONS

[1]Martin Luther University, Halle, Germany
[2]University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[3]University Hospitals and KU Leuven, Leuven, Belgium
[4]Queen Elizabeth Hospital, Woodville, South Australia, Australia
[5]Universitaetsmedizin Mannheim, Mannheim, Germany
[6]CHU Ambroise Paré, Assistance Publique-Hôpitaux de Paris, Boulogne-Billancourt, France
[7]Université Catholique de Louvain, CHU-UCL-Namur (Sainte-Elisabeth), Namur, Belgium
[8]AZ Turnhout, Turnhout, Belgium
[9]Institute of Oncology, Davidoff Center, Rabin Medical Center, Petah Tikva, Israel
[10]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[11]Leopoldina-Krankenhaus der Stadt Schweinfurt gGmbH, Schweinfurt, Germany
[12]Allgemeines Krankenhaus Celle, Celle, Germany
[13]Klinikum Ludwigsburg, Ludwigsburg, Germany
[14]Onkologische Schwerpunktpraxis, Hanau, Germany
[15]Gemeinschaftspraxis Haematologie und Onkologie, Bottrop, Germany
[16]Alfred Health and School of Public Health, Monash University, Melbourne, Victoria, Australia
[17]Austin-Health, Heidelberg, Victoria, Australia
[18]European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium
[19]Caritasklinikum, Saarbrucken, Germany

CORRESPONDING AUTHOR

Hans-Joachim Schmoll, MD, PhD, Clinic for Internal Medicine IV–Hematology/Oncology, University Clinic, Martin Luther University Halle-Wittenberg, Ernst-Grube Str 40, 06120 Halle (Saale), Germany; e-mail: hans-joachim.schmoll@uk-halle.de.

PRIOR PRESENTATION

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CLINICAL TRIAL INFORMATION

NCT00766155 (PETACC-6)

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AUTHOR CONTRIBUTIONS

Conception and design: Hans-Joachim Schmoll, Eric Van Cutsem, Timothy Price, Bernard Nordlinger, John Zalcberg, Karin Haustermans
Administrative support: Hans-Joachim Schmoll, Bernard Nordlinger, Stephan Hollerbach, Sandrine Marreaud, Manfred P. Lutz
Provision of study material or patients: Hans-Joachim Schmoll, Eric Van Cutsem, Timothy Price, Ralf D. Hofheinz, Baruch Brenner, Karel Caca, Niall Tebbutt, Sandrine Marreaud, Manfred P. Lutz, Karin Haustermans
Collection and assembly of data: Hans-Joachim Schmoll, Alexander Stein, Eric Van Cutsem, Ralf D. Hofheinz, Bernard Nordlinger, Jean-François Daisne, Jos Janssens, Baruch Brenner, Hans Reinel, Stephan Hollerbach, Karel Caca, Florian Fauth, Niall Tebbutt, Sandrine Marreaud, Manfred P. Lutz
Data analysis and interpretation: Hans-Joachim Schmoll, Alexander Stein, Eric Van Cutsem, Timothy Price, Ralf D. Hofheinz, John Zalcberg, Niall Tebbutt, Murielle E. Mauer, Sandrine Marreaud, Manfred P. Lutz, Karin Haustermans
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Pre- and Postoperative Capecitabine Without or With Oxaliplatin in Locally Advanced Rectal Cancer: PETACC 6 Trial by EORTC GITCG and ROG, AIO, AGITG, BGDO, and FFCD

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Hans-Joachim Schmoll
Consulting or Advisory Role: Roche, SERVIER, Amgen, Astellas Pharma, TREOS, Enterome
Research Funding: Bristol Myers Squibb (Inst), Merck KGaA (Inst), SERVIER (Inst), Roche (Inst), Genentech (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: Roche, Amgen, Bristol Myers Squibb, SERVIER

Alexander Stein
Consulting or Advisory Role: Merck KGaA, Bristol Myers Squibb, Amgen, Roche, MSD, SERVIER, AstraZeneca
Speakers' Bureau: Roche, Sanofi, Bayer AG, Eli Lilly, Celgene, Amgen, Merck KGaA, SERVIER, Bristol Myers Squibb
Research Funding: Roche (Inst), Sanofi (Inst), Merck KGaA (Inst), Bristol Myers Squibb (Inst), SERVIER (Inst)
Travel, Accommodations, Expenses: Roche, Bristol Myers Squibb, Merck KGaA

Eric Van Cutsem
Consulting or Advisory Role: Bayer AG, Eli Lilly, Roche, SERVIER, Bristol Myers Squibb, Celgene, Merck Sharp & Dohme, Merck KGaA, Novartis, AstraZeneca, Halozyme, Array BioPharma, Biocartis, GlaxoSmithKline, Daiichi Sankyo, Pierre Fabre, Sirtex, Taiho, Incyte
Research Funding: Amgen (Inst), Bayer AG (Inst), Boehringer Ingelheim (Inst), Eli Lilly (Inst), Novartis (Inst), Roche (Inst), Celgene (Inst), Ipsen (Inst), Merck (Inst), Merck KGaA (Inst), SERVIER (Inst), Bristol Myers Squibb (Inst)

Timothy Price
Consulting or Advisory Role: Amgen, Roche (Inst), Merck Serono (Inst)
Research Funding: Amgen (Inst)
Travel, Accommodations, Expenses: Amgen

Ralf D. Hofheinz
Honoraria: Roche, Amgen, Merck Serono, Sanofi, MSD, Bristol Myers Squibb, Eli Lilly, Medac, SERVIER, AstraZeneca
Consulting or Advisory Role: Merck Serono, Amgen, Roche, Sanofi, Bristol Myers Squibb, MSD, SERVIER
Speakers' Bureau: Roche, Sanofi, Eli Lilly, Merck, Amgen, SERVIER, MSD, Bristol Myers Squibb
Research Funding: Sanofi (Inst), Medac (Inst), Deutsche Kresbhilfe (Inst)

Baruch Brenner
Honoraria: MSD Oncology, Bristol Myers Squibb, Roche
Consulting or Advisory Role: MSD Oncology, Boehringer Ingelheim
Research Funding: Merck Serono, Bristol Myers Squibb
Travel, Accommodations, Expenses: Bristol Myers Squibb, Roche, Merck Serono

Stephan Hollerbach
Research Funding: Interscope (Inst)

Carla V. Hannig
Honoraria: Roche, Takeda Pharmaceuticals, Boehringer Ingelheim, Novartis
Travel, Accommodations, Expenses: Celgene, Novartis

John Zalcberg
Stock and Other Ownership Interests: GW Pharmaceuticals, Aimmune, Vertex, Alnylam, Biomarin, Ophthea, Amarin, Concert Pharmaceuticals, Frequency Therapeutics, Global Blood Therapeutics, Gilead Sciences, Madrigal Pharmaceuticals, UniQure, Sangamo Biosciences, Acceleron Pharmaceuticals, Zogenix, Myovant Sciences, Orphazyme, Moderna Therapeutics
Honoraria: Pfizer, Specialized Therapeutics, Merck Serono, Targovax, Halozyme, Gilead Sciences, Novella Clinical
Consulting or Advisory Role: Pfizer, Merck Serono, Targovax, Merck Sharp & Dohme, Sirtex Medical, Halozyme, Lipotek, Specialized Therapeutics, CEND
Research Funding: Bayer AG (Inst), Merck Serono (Inst), Roche (Inst), Bristol Myers Squibb (Inst), Pfizer (Inst), AstraZeneca (Inst), Specialized Therapeutics (Inst), Baxalta (Inst), Shire (Inst), Eli Lilly (Inst)
Travel, Accommodations, Expenses: Merck Serono, AstraZeneca, Merck Sharp & Dohme, Deciphera

Niall Tebbutt
Honoraria: Roche, Bristol Myers Squibb
Consulting or Advisory Role: Roche, Bristol Myers Squibb
Research Funding: Bristol Myers Squibb (Inst)
Travel, Accommodations, Expenses: Bayer AG

Manfred P. Lutz
Speakers' Bureau: SERVIER, Eli Lilly
Research Funding: SERVIER (Inst)

Karin Haustermans
Honoraria: Varian Medical Systems
Research Funding: Varian Medical Systems

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APPENDIX

Specifications of Statistical Analysis

The primary efficacy analyses for this trial were done in all randomly assigned patients according to the intention-to-treat principle. After a median follow-up of 64 months, disease-free survival (DFS) and overall survival (OS) were compared using the Cox proportional hazards regression model adjusted for all stratification factors except center as the primary method of analysis. DFS and OS rates, Kaplan-Meier method, and treatment effects were summarized with hazard ratios and respective 95% CIs. The cumulative incidences of locoregional and distant failures were estimated and compared between arms using the competing-risk methodology, with death in the absence of an event treated as a competing risk. Differences between arms were tested using the Fine and Gray model adjusted for all stratification factors but center. For end points pertaining to the patients' surgical outcome, the event rates were compared between arms using a logistic regression model adjusted for all stratification factors but center. Patients not operated on or not receiving a resection were scored as having experienced treatment failure in these analyses.

Possible heterogeneity of the results was investigated by performing subgroup analyses. Heterogeneity was tested by means of a Cochran's Q test. Graphical displays of the results are provided as Forest plots.

A multivariable prognostic analysis was performed on DFS using Cox proportional hazards regression models. The analysis was restricted to the per-protocol population (pooled treatment arms). Interactions of baseline factors with treatment arm were added in the model to allow the identification of possible predictive factors of treatment benefit. For the model building, Collett's model selection approach was used with a level of significance of .1 for the univariable screening and entry and stay criteria of .05 (Collett D: *Modelling Survival Data in Medical Research*, 1994). The safety analyses were performed on all patients who had started their allocated treatment. All statistical analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC).

Trial 40054: List of Participating Centers

Name	Participating Center	Country
Gill, Sanjeev	Alfred Hospital	Australia
Tebbutt, Niall	Austin Hospital	Australia
Asghari, Ray	Bankstown-Lidcombe Hospital	Australia
Blum, Robert	Bendigo Hospital	Australia
Briscoe, Karen	Coffs Harbor Health Campus	Australia
Karapetis, Chris	Flinders Medical Centre	Australia
Ng, Weng	Liverpool Hospital	Australia
Begbie, Stephen	Port Macquarie Base Hospital	Australia
Goldstein, David	Prince of Wales Hospital	Australia
Walpole, Euan	Princess Alexandra Hospital	Australia
Price, Timothy	The Queen Elizabeth Hospital	Australia
Singhal, Nimit	Royal Adelaide Hospital	Australia
Burge, Matthew	Royal Brisbane and Women's Hospital	Australia
Byard, Ian	Royal Hobart Hospital	Australia
Hruby, George	Royal Prince Alfred Hospital	Australia
Ng, Siobhan	St John of God Hospital, Subiaco	Australia
Lynch, Rod	Geelong Hospital-Andrew Love Cancer Centre	Australia
Sabesan, Sabe	Townsville General Hospital	Australia
Monsaert, Els	AZ Maria Middelares	Belgium
Vanderstraeten, Erik	AZ Maria Middelares	Belgium
Ferrante, Michel	AZ Sint-Maarten	Belgium
Janssens, Jozef	AZ Turnhout-Campus Sint Elisabeth	Belgium
Martens, Michel	AZ Turnhout-Campus Sint Elisabeth	Belgium
Baudoux, Etienne	CHU Sart-Tilman	Belgium
Polus, Marc	CHU Sart-Tilman	Belgium
Rezaei Kalantari, Hassan	Centre Hospitalier Regional Verviers	Belgium
Kerger, Joseph	CHU Mont Godinne-UCL Namur	Belgium

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Name	Participating Center	Country
Daisne, Jean-François	CHU Site Sainte-Elisabeth-UCL Namur	Belgium
Weytjens, Reinhilde	GasthuisZusters Antwerpen-Sint-Augustinus	Belgium
Delaunoit, Thierry	Hopital De Jolimont	Belgium
Peeters, Marc	Universitair Ziekenhuis Antwerpen	Belgium
Van Den Brande, Jan	Universitair Ziekenhuis Antwerpen	Belgium
Laurent, Stéphanie	Universitair Ziekenhuis Gent	Belgium
Van Den Weyngaert, Danielle	ZNA Middelheim	Belgium
Vanderkam, Sabine	ZNA Middelheim	Belgium
Schrijvers, Dirk	ZNA Middelheim	Belgium
Martin, Philippe	Centre Bourgogne	France
Crehange, Gilles	Centre Georges-François-Leclerc	France
Truc, Gilles	Centre Georges-François-Leclerc	France
Karine, Peignaux	Centre Georges-François-Leclerc	France
Maingon, Philippe	Centre Georges-François-Leclerc	France
Artignan, Xavier	Centre Hospitalier Prive Saint-Gregoire	France
Desseigne, Françoise	Centre Leon Berard	France
Martel-Lafay, Isabelle	Centre Leon Berard	France
Latrive, Jean-Paul	CH de Compiegne	France
Bosset, Jean-François	CHRU de Besancon-Hopital Jean Minjoz	France
Nguyen, Thierry	CHRU de Besancon-Hopital Jean Minjoz	France
Etienne, Pierre	Clinique Armoricaine De Radiologie	France
Ducreux, Michel	Gustave Roussy	France
Seitz, Jean-François	Hôpital de La Timone (APHM)	France
Ben Abdelghani, Meher	Institut de Cancerologie Strasbourg Europe (formerly Paul Strauss)	France
Freier, Werner	Onkologie im Medicinum	France
Hollerbach, Stephan	Allgemeines Krankenhaus Celle	Germany
Peters, Uwe	Ambulantes Tumorzentrum Spandau	Germany
Holtkamp, Wilhelm	Ammerland-Klinik GmbH-Universitaet Goettingen	Germany
Speidel, Andrea	Arztefor. Hennigsdor	Germany
Thiemann, Roland	Asklepios Klinik Weissenfels	Germany
Behringer, Dirk	Augusta-Kranken-Anstalt	Germany
Gaska, Tobias	Bruederkrankenhaus St Josef Paderborn	Germany
Kremers, Stephan	Caritas KRHS Lebach	Germany
Matzdorf, Axel	CaritasKlinikum Saarbruecken St Theresia	Germany
Moser, Lutz	Charite-Universitaetsmedizin Berlin-Campus Benjamin Franklin	Germany
Mueller-Naendrup, Clemens	Darmzentrum Suedwestfalen, Katholische Hospitalgesellschaft	Germany
Pflueger, Karl-Heinz	Ev Diakonie-Krankenhaus gGmbH	Germany
Reymond, Marc Andre	Ev Johannes-Krankenhaus	Germany
Potenberg, Jochem	Ev Waldkrankenhaus Spandau	Germany
Baake, Gerold	Facharzt fuer Innere Medizin	Germany
Esser, Martin	Facharzt fuer Innere Medizin	Germany
Held, Harald	Friedrich-Ebert-Krankenhaus	Germany
Soeling, Ulrike	Gemeinschaftspraxis	Germany

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Name	Participating Center	Country
Dingeldein, Gerrit	Gemeinschaftspraxis-Darmstadt	Germany
Bangerter, Markus	Gemeinschaftspraxis Augsburg	Germany
Jacobasch, Lutz	Gemeinschaftspraxis Dresden	Germany
Hannig, Carla Verena	Gemeinschaftspraxis Haematologie und Onkologie	Germany
Reiser, Marcel	Gemeinschaftspraxis Katay/Reiser	Germany
Schmidt, Burkhard	Gemeinschaftspraxis Muenchen	Germany
Tschechne, Barbara	Gemeinschaftspraxis Tschechne/Luft für Innere Medizin	Germany
Bertram, Mathias	Gemeinschaftspraxis-Hamburg	Germany
Brinkmann, Lutz	Gemeinschaftspraxis-Laatzen	Germany
Forstbauer, Helmut	Gesellschaft für onkologische Studien, Praxismanagement und Logistik	Germany
Engel, Erik	Haematologisch-Onkologische Praxis Altona	Germany
Hegewisch-Becker, Susanna	Haematologisch-Onkologische Praxis Eppendorf	Germany
Van Roye, V.	Haematologisch-Onkologische Praxis-Koblenz	Germany
Boicev, Alexander	Heinrich-Braun-Krankenhaus	Germany
Alberti, Winfried	Helios Klinikum Wuppertal	Germany
Halm, Ulrich	Helios Park-Klinikum Leipzig	Germany
Boldt, Thomas	Hospital Dresden-Friedrichstadt	Germany
Reeb, Manfred	Institut für Medizinische Dokumentation, Gutachtenerstellung, Gesundheitsfoerderung und Qualitaetssicherung GbR	Germany
Niedermeier, Michael	Internistische Gemeinschaftspraxis- Memmingen	Germany
Hoesl, Mark	Internistische Gemeinschaftspraxis-Nuernberg	Germany
Frank-Gleich, Stefanie	Internistisch-Onkologische Gemeinschaftspraxis	Germany
Ko, Yon	Johanniter-Krankenhaus Bonn	Germany
Hennemann, Burkhard	Johanniter-Krankenhaus Rheinhausen	Germany
Doerner, Arnulf	KKH Alten Eichen	Germany
Fischbach, Cathie	Klinikum Aschaffenburg	Germany
Huegle, Ulrich	Kliniken der Stadt Koeln-Krankenhaus Holweide	Germany
Schlichthaerle, Tessa	Kliniken der Stadt Koeln-Krankenhaus Holweide	Germany
Stahl, Michael Konrad	Kliniken Essen-Mitte	Germany
Kuckhoff, Michael	Klinikum Barnim GmbH	Germany
Hielscher, Joerg	Klinikum Chemnitz gGmbH	Germany
Wagner, Siegfried	Klinikum Deggendorf	Germany
Brugger, Wolfram	Klinikum Der Stadt Villingen-Schwenningen	Germany
Baeumer, Sabine	Klinikum Dortmund gGmbH	Germany
Lambertz, Helmut	Klinikum Garmisch-Partenkirchen	Germany
Burk, Martin	Klinikum Hanau	Germany
Gruenewald, Martin	Klinikum Heidenheim	Germany
Roemmele, U.	Klinikum Kirchheim-Nuertingen	Germany
Bildat, Stephan	Klinikum Kreis Herford	Germany
Kempf, Barbara	Klinikum Landshut	Germany
Constantin, Christian	Klinikum Lippe Lemgo	Germany
Caca, Karel	Klinikum Ludwigsburg	Germany
Wilhelm, Martin	Klinikum Nuernberg-Standort Nord	Germany
Hebart, Holger	Klinikum Schwaebisch-Gmuend	Germany

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Name	Participating Center	Country
Leser, Hans-Georg	Klinikum Sindelfingen-Boeblingen	Germany
Fischer von Weikersthal, Ludwig	Klinikum St Marien	Germany
Mergenthaler, Hans-Guenther	Klinikum Stuttgart-Katharinenhospital	Germany
Schmiegel, Wolff	Knappschaft Krankenhaus	Germany
Trenn, Guido	Knappschaftskrankenhaus Bottrop	Germany
Krummenerl, Patrick	Krankenhaus Martha-Maria Halle Doelau gGmbH	Germany
Dencausse, Yves	Krankenhaus Siloah	Germany
Kirchner, Hartmut; Wildfang, I.	Krankenhaus Siloah-Klinikum Region Hannover GmbH	Germany
Gosenheimer, Robert	Krankenhaus St Marienwoerth	Germany
Grunewald, Martina	Kreisklinik Aschersleben-Stassfurt gGmbH	Germany
Sieber, Markus	Kreiskrankenhaus Gummersbach GmbH	Germany
Reinel, Hans	Leopoldina-Krankenhaus der Stadt Schweinfurt gGmbH	Germany
Lindemann, W.	Marienhospital	Germany
Denzlinger, Claudio	Marienhospital Stuttgart	Germany
Hapke, Gunnar	Marienkrankenhaus	Germany
Arnold, Dirk	Martin Luther Universitaet-Universitaetsklinikum Halle (Saale)	Germany
Schmoll, Hans-Joachim	Martin Luther Universitaet-Universitaetsklinikum Halle (Saale)	Germany
Koenigsmann, Michael	Mediprojekt GbR-Hannover	Germany
Clemens, Michael	Mutterhaus Der Borromaerinnen	Germany
Mahlberg, Rolf	Mutterhaus Der Borromaerinnen	Germany
Demandt, Matthias	MVZ Klinikum Straubing GmbH	Germany
Grossmann, Johannes	Notdienstpraxis am Evangelischen Krankenhaus Bethesda	Germany
Eggert, Jochen	OnkoLog Moers GbR	Germany
Mueller, Lothar	Onkologie UnterEms, Leer-Papenburg-Emden	Germany
Welslau, Manfred	Onkologische Gemeinschaftspraxis	Germany
Behrens, Ruediger	Onkologische Praxis Halle	Germany
Schieder, Heike	Onkologische Praxis im Krankenhaus Buchholz	Germany
Nusch, Arnd	Onkologische Praxis Velbert	Germany
Grundeis, Marc	Onkologische Schwerpunktpraxis	Germany
Rauh, Jacqueline	Onkologische Schwerpunktpraxis Dr Koch	Germany
Ladda, Ekkehart	Onkologische Schwerpunktpraxis Neumarkt	Germany
Fauth, Florian	Onkologische Schwerpunktpraxis-Hanau	Germany
Goehler, Thomas	Onkozentrum Dresden/Freiberg	Germany
Woerdehoff, Herbert	Otto-Von-Guericke-Universitaet Magdeburg-Universitaetsklinik	Germany
Geiger, Matthias	Paracelsius Krankenhaus	Germany
Breuer, Friedhelm	PIOH Gemeinschaftspraxis	Germany
Peveling Reddemann, Christina	Praxis-Leverkusen	Germany
Marquard, Felix	Praxis Dr Marquard	Germany
Schroeder, Detlev	Praxis Dr Schroeder	Germany
Schmitz, Stephan	Praxis Drs Schmitz/Steinmetz	Germany
Dietze, Lutz	Praxis fuer Haematologie und Internistische Onkologie	Germany
Schliesser, Georg Christian	Praxis fuer Haematologie und Internistische Onkologie	Germany
Papke, Jens	Praxis Innere Medizin-Neustadt	Germany

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Name	Participating Center	Country
Schwerdtfeger, Michael	Praxis Koethen	Germany
Groschek, Mathias	Praxis Wuerselen	Germany
Hoehler, Thomas	Prosper-Hospital Recklinghausen	Germany
Grabenbauer, Gerhard	Regiomed Kliniken Coburg	Germany
Puchtler, Gerhard	RoMed Klinikum Rosenheim	Germany
Schmoecker, Christoph	Sana Klinikum Berlin Lichtenberg	Germany
Tajrobehkar, Kian	Sankt Elisabeth Krankenhaus	Germany
Seipelt, Gernot	Schwerpunktpraxis und Tagesklinik	Germany
Martens, Uwe	SLK-Kliniken Heilbronn	Germany
Schlegel, Frank	St Antonius Hospital	Germany
Kaiser, Ulrich	St Bernward Krankenhaus Hildesheim	Germany
Greeve, Jobst	St Vincenz Krankenhaus Paderborn	Germany
Koch, Bernhard	St Vincenz-Krankenhaus Datteln	Germany
Teschendorf, Christian	St-Josefs-Hospital	Germany
Staiger, Hans-Juergen	Stadtklinik Baden-Baden	Germany
Guenther, Barbara	Staedtisches Kliniken Duesseldorf-Benrath	Germany
Schmidt, Peter	Staedtisches Klinikum Neunkirchen	Germany
Grothe, Wilfried	Staedtisches Klinikum	Germany
Hoeffkes, Heinz-Gert	Staedtisches Klinikum	Germany
Deckert, Markus	Staedtisches Klinikum Brandenburg GmbH	Germany
Guenter, Andreas	Staedtisches Klinikum Braunschweig gGmbH	Germany
Florschuetz, Axel	Staedtisches Klinikum Dessau	Germany
Naumann, Ralph	Stiftungsklinikum Mittelrhein	Germany
Vehling-Kaiser, Ursula	Tagesklinik Landshut	Germany
Eble, Michael	Universitaetsklinikum Aachen AOR-Medizinische Fakultaet der RWTH	Germany
Folprecht, Gunnar	Universitaetsklinikum Carl Gustav Carus	Germany
Lindig, Udo	Universitaetsklinikum Jena	Germany
Koelbl, Oliver	Universitaetsklinikum Regensburg	Germany
Hildebrandt, Guido	Universitaetsklinikum Rostock-Zentrum fur Radiologie mit Klinik und Poliklinik fur Strahlentherapie	Germany
Block, Andreas	Universitaets-Krankenhaus Eppendorf	Germany
Hofheinz, Ralf Dieter	UniversitaetsMedizin Mannheim	Germany
de Wit, Maike	Vivantes Klinikum Neukoelln	Germany
Spaeth-Schwalbe, Ernst	Vivantes Klinikum Spandau	Germany
Link, Hartmut	Westpfalz-Klinikum Gmbh	Germany
Fronhoffs, Stefan	Zentrum fuer ambulante Haematologie & Onkologie	Germany
Brenner, Baruch	Rabin Medical Center-Tel Aviv	Israel
Ben-Yosef, Rahamim	Rambam Health Care Campus, Oncology Institute	Israel
Shulman, Katerina	Rambam Health Care Campus, Oncology Institute	Israel
Jeffery, Mark	Christchurch Hospital	New Zealand

TABLE A1. Correlation Between Dose Reduction or Withdrawal of Capecitabine and/or Oxaliplatin Because of Toxicity and Surgical Outcome

Variable	Dose Reduction or Withdrawal for Toxicity, No. (%)		Total, No. (%)
	No	Yes	
No. of patients	345	202	547
Total mesorectal excision	281 (81.4)	281 (81.4)	281 (81.4)
R0 (complete)	320 (92.8)	320 (92.8)	320 (92.8)
Pathologic complete remission	45 (13.0)	45 (13.0)	45 (13.0)

TABLE A2. Seven-Year DFS and OS According to Application Versus No Application of Adjuvant Chemotherapy by German and Non-German Patient Population

		Cape + RT, %		CAPOX + RT, %			
Application of Adjuvant Chemotherapy	**No. of Patients**	**Patient Rate**	**Rate at 7 Years**	**Patient Rate**	**Rate at 7 Years**	**HR (95% CI)**	***P***
DFS							
All patients	1,094		66.1		65.5	1.03 (0.83 to 1.29)	.786
Stage II	236	21.2	60.1	21.9	62.1	0.95 (0.59 to 1.51)	.818
Stage III	778	71.7	67.9	70.6	66.8	1.04 (0.79 to 1.36)	.784
Chemotherapy yes[a]	803	77.0	72.3	69.8	71.8	0.97 (0.73 to 1.30)	.850
Stage II	178	22.1	75.0	22.3	65.7	1.15 (0.64 to 2.09)	.635
Stage III	572	71.3	71.4	71.2	73.2	0.92 (0.65 to 1.30)	.644
Chemotherapy no[b]	217	18.6	45.8	21.0	53.2	0.98 (0.65 to 1.48)	.922
Stage II	41	17.6	0.0	20.0	50.7	0.63 (0.25 to 1.60)	.330
Stage III	158	74.5	58.3	71.3	55.2	1.15 (0.70 to 1.89)	.586
Germany: all	737	66.7	69.2	68.0	62.3	1.27 (0.96 to 1.67)	.092
Stage II	172	24.1	50.0	22.6	56.2	0.83 (0.47 to 1.46)	.519
Stage III	494	66.6	75.8	67.5	66.3	1.44 (1.02 to 2.03)	.038
Chemotherapy yes	543	80.0	79.2	67.5	68.5	1.27 (0.89 to 1.82)	.186
Stage II	130	23.6	76.9	24.3	58.5	1.18 (0.58 to 2.43)	.650
Stage III	366	68.2	80.6	66.5	73.7	1.33 (0.85 to 2.08)	.204
Chemotherapy no	148	17.3	20.5	22.8	49.5	0.83 (0.52 to 1.34)	.449
Stage II	31	25.4	0.0	17.6	62.2	0.33 (0.10 to 1.07)	.053
Stage III	128	61.9	55.6	72.9	49.9	1.15 (0.62 to 2.14)	.652
Outside Germany: all	357	33.3	61.3	32.0	71.0	0.70 (0.47 to 1.02)	.061
Stage II	64	15.4	66.7	20.6	64.1	1.25 (0.53 to 2.92)	.609
Stage III	284	81.9	60.1	77.1	71.5	0.61 (0.40 to 0.96)	.029
Chemotherapy yes	260	70.9	63.9	74.9	77.0	0.59 (0.36 to 0.96)	.032
Stage II	48	18.6	69.6	18.3	73.5	1.08 (0.38 to 3.08)	.885
Stage III	206	78.3	61.3	80.2	77.0	0.51 (0.29 to 0.90)	.017
Chemotherapy no	69	21.4	64.2	17.1	62.1	1.11 (0.50 to 2.48)	.799
Stage II	10	5.1	—	26.7	—	—	—
Stage III	57	94.9	62.4	66.7	69.1	0.81 (0.31 to 2.13)	.669
OS							
All patients	1,094		73.5		73.7	1.19 (0.91 to 1.57)	.205
Stage II	236	21.2	57.5	21.9	71.9	0.95 (0.55 to 1.63)	.843
Stage III	778	71.7	78.9	70.6	74.6	1.21 (0.86 to 1.69)	.274
Chemotherapy yes	803	77.0	76.7	69.8	81.9	0.98 (0.67 to 1.44)	.919
Stage II	178	22.1	67.1	22.3	76.3	1.23 (0.59 to 2.59)	.582
Stage III	572	71.3	80.6	71.2	83.5	0.83 (0.52 to 1.33)	.444
Chemotherapy no	217	18.6	63.4	21.0	55.7	1.24 (0.76 to 2.02)	.387
Stage II	41	17.6	0.0	20.0	62.2	0.47 (0.17 to 1.26)	.123
Stage III	158	74.5	78.0	71.3	55.3	1.84 (0.98 to 3.48)	.056

Abbreviations: Cape, capecitabine; CAPOX, capecitabine and oxaliplatin; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RT, radiotherapy.

[a]Patients operated within protocol who started adjuvant chemotherapy.

[b]Patients operated within protocol who did not start adjuvant chemotherapy.

TABLE A3. Baseline and Treatment Characteristics of Patients Enrolled at German and Non-German Sites

Characteristic	Country, No. (%)	
	Outside Germany	Germany
No. of patients	357	737
Median age, years (range)	61 (26-87)	62 (23-84)
Sex		
Male	248 (69.5)	526 (71.4)
Female	109 (30.5)	211 (28.6)
ECOG PS		
0	282 (79.0)	570 (77.3)
1	74 (20.7)	160 (21.7)
2	1 (0.3)	7 (0.9)
cT		
cT1	0 (0.0)	5 (0.7)
cT2	21 (5.9)	48 (6.5)
cT3	305 (85.4)	630 (85.5)
cT4	31 (8.7)	54 (7.3)
cN		
cN0	64 (17.9)	174 (23.6)
cN1	195 (54.6)	396 (53.7)
cN2	90 (25.2)	101 (13.7)
cNX	8 (2.2)	66 (9.0)
TNM stage		
II	64 (17.9)	172 (23.3)
III	284 (79.6)	494 (67.0)
cT3-4, cNX	8 (2.2)	65 (8.8)
Missing	1 (0.3)	6 (0.8)
Distance of tumor to anal verge, cm		
≤ 5	167 (46.8)	306 (41.5)
> 5	190 (53.2)	431 (58.5)
MRI available at the center		
No	36 (10.1)	86 (11.7)
Yes	321 (89.9)	651 (88.3)
Locoregional staging performed by		
EUS + MRI	129 (36.1)	324 (44.0)
EUS + CT scan	67 (18.8)	332 (45.0)
MRI alone	161 (45.1)	81 (11.0)
Adjuvant chemotherapy started		
Cape + RT	129 (70.9)	292 (80.0)
CAPOX + RT	132 (75.4)	251 (67.5)

Abbreviations: Cape, capecitabine; CAPOX, capecitabine and oxaliplatin; CT, computed tomography; EUS, endorectal ultrasound; MRI, magnetic resonance imaging; RT, radiotherapy.

TABLE A4. Multivariable Prognostic Model for DFS in the Per-Protocol Population

Baseline Factor	HR (95% CI)	*P* (*df*)
Treatment arm		
Cape + RT	1.00	.914 (1)
CAPOX + RT	0.99 (0.78 to 1.24)	
Age, years		
≤ 60	1.00	.030 (1)
> 60	1.30 (1.03 to 1.64)	
cT		
cT1-cT2	1.00	.044 (2)
cT3	1.67 (0.96 to 2.92)	.071
cT4	2.31 (1.19 to 4.48)	.013
Sphincter preservation according to the surgeon		
Not sphincter preserving	1.00	.032 (1)
Sphincter preserving	0.76 (0.59 to 0.98)	

NOTE. The per-protocol population included all eligible patients who started their allocated treatment.
Abbreviations: Cape, capecitabine; CAPOX, capecitabine and oxaliplatin; DFS, disease-free survival; HR, hazard ratio; RT, radiotherapy.

TABLE A5. Treatment Benefit by Predictive Factor Level Adjusted for Identified Prognostic Factors

	Treatment Benefit for Perioperative Oxaliplatin[a]		Test for Predictive Value (interaction)[a]
Country	HR (95% CI)[b]	*P*	*P*
Germany	1.19 (0.90 to 1.59)	.2243	.0289
Not Germany	0.69 (0.47 to 1.03)	.0692	

Abbreviation: HR, hazard ratio.
[a]Treatment benefit computed from the multivariable model with prognostic factors age, cT, sphincter preservation according to the surgeon, country (Germany *v* not Germany), treatment arm, and the interaction of country (Germany *v* not Germany) and treatment arm.
[b]Capecitabine and oxaliplatin plus radiotherapy/capecitabine plus radiotherapy.

TABLE A6. Phase III Trials Evaluating the Role of Oxaliplatin-Based Chemoradiation Therapy and Postoperative Chemotherapy

	Trial				
Criterion	**STAR 1**	**ACCORD 12/0405-Prodige 2**	**NSABP R04**	**CAO/ARO/AIO-04**	**PETACC 6**
Stage at inclusion	T3/4 and/or N+	≥ T3 or ≥ T2 lower rectum	T3/4 and/or N+	T3/4 and/or N+	T3/4 and/or N+
Primary end point	OS	pCR	Local relapse, pCR, sphincter-preserving surgery	DFS	DFS
No. of patients	747	598	1,608	1,236	1,094
Chemotherapy regimen	5FU 225 mg/m^2/d *v* 5FUOX 60 mg/m^2 weekly × 6	Cape 800 mg/m^2 twice a day *v* CAPOX 50 Gy/Cape + Ox 50 mg/m^2 weekly × 5	5FU 225 mg/m^2/d and Cape 825 mg/m^2 twice a day *v* 5FU or CAPOX 50 mg/m^2 weekly × 5	5FU 1,000 mg/m^2 days 1-5 and 29-33 *v* 5FU 250 mg/m^2 days 1-14 and 22-35 + Ox 50 mg/m^2 days 1, 8, 22, and 29[a]	Cape 825 mg/m^2 twice a day *v* CAPOX with Cape 825 mg/m^2 + Ox 50 mg/m^2 weekly × 5
RT dose, Gy (fractions)	50.4 (1.8)	Cape: 45 (1.8) CAPOX: 50 (2)	45 + 5.4 or 10.8 boost (1.8)	50.4 (1.8)	45 (1.8); 50.4 (1.8)
Grade 3/4 toxicity, %	8 *v* 24; $P < .001$	11 *v* 25; $P < .001$	28 *v* 40	20 *v* 23	23.6 *v* 46.3
pCR rate, %	16 *v* 16; $P = .9$	13.9 *v* 19.2; $P = .09$	17.8 *v* 19.5; $P = .42$	13 *v* 17; $P = .038$	11.5 *v* 13.5; $P = .31$
Adjuvant treatment	Any 5FU based	Open	Open	5FU *v* FOLFOX	Cape *v* CAPOX
3- or 5-year DFS	NA	3-year: 67.9% *v* 72.7%; HR, 0.88; $P = .39$	5-year: 64.2% *v* 69.2%; HR, 0.91; $P = .34$	3-year: 71.2% *v* 75.9%; HR, 0.79; $P = .03$	5-year: 71.3% *v* 70.5%; HR, 1.03; $P = .78$
3- or 5-year OS	NA	3-year: 87.6% *v* 88.3%; HR, 0.94; NS	5-year: 79% *v* 81.3%; HR, 0.89; $P = .38$	3-year: 88.0% *v* 88.7%; HR, 0.96; NS	5-year: 83.1% *v* 80.1%; HR, 1.19; $P = .2$

Abbreviations: 5FU, fluorouracil; 5FUOX, fluorouracil and oxaliplatin; Cape, capecitabine; CAPOX, capecitabine and oxaliplatin; DFS, disease-free survival; FOLFOX; infusional fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; NA, not applicable; NS, not significant; OS, overall survival; Ox, oxaliplatin; pCR, pathologic complete remission; RT, radiotherapy.