

Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial

Ralf-Dieter Hofheinz, Frederik Wenz, Stefan Post, Axel Matzdorff, Stephan Laechelt, Jörg T Hartmann, Lothar Müller, Hartmut Link, Markus Moehler, Erika Kettner, Elisabeth Fritz, Udo Hieber, Hans Walter Lindemann, Martina Grunewald, Stephan Kremers, Christian Constantin, Matthias Hipp, Gernot Hartung, Deniz Gencer, Peter Kienle, Iris Burkholder, Andreas Hochhaus

Summary

Background Fluorouracil-based chemoradiotherapy is regarded as a standard perioperative treatment in locally advanced rectal cancer. We investigated the efficacy and safety of substituting fluorouracil with the oral prodrug capecitabine.

Methods This randomised, open-label, multicentre, non-inferiority, phase 3 trial began in March, 2002, as an adjuvant trial comparing capecitabine-based chemoradiotherapy with fluorouracil-based chemoradiotherapy, in patients aged 18 years or older with pathological stage II–III locally advanced rectal cancer from 35 German institutions. Patients in the capecitabine group were scheduled to receive two cycles of capecitabine (2500 mg/m² days 1–14, repeated day 22), followed by chemoradiotherapy (50·4 Gy plus capecitabine 1650 mg/m² days 1–38), then three cycles of capecitabine. Patients in the fluorouracil group received two cycles of bolus fluorouracil (500 mg/m² days 1–5, repeated day 29), followed by chemoradiotherapy (50·4 Gy plus infusional fluorouracil 225 mg/m² daily), then two cycles of bolus fluorouracil. The protocol was amended in March, 2005, to allow a neoadjuvant cohort in which patients in the capecitabine group received chemoradiotherapy (50·4 Gy plus capecitabine 1650 mg/m² daily) followed by radical surgery and five cycles of capecitabine (2500 mg/m² per day for 14 days) and patients in the fluorouracil group received chemoradiotherapy (50·4 Gy plus infusional fluorouracil 1000 mg/m² days 1–5 and 29–33) followed by radical surgery and four cycles of bolus fluorouracil (500 mg/m² for 5 days). Patients were randomly assigned to treatment group in a 1:1 ratio using permuted blocks, with stratification by centre and tumour stage. The primary endpoint was overall survival; analyses were done based on all patients with post-randomisation data. Non-inferiority of capecitabine in terms of 5-year overall survival was tested with a 12·5% margin. This trial is registered with ClinicalTrials.gov, number NCT01500993.

Findings Between March, 2002, and December, 2007, 401 patients were randomly allocated; 392 patients were evaluable (197 in the capecitabine group, 195 in the fluorouracil group), with a median follow-up of 52 months (IQR 41–72). 5-year overall survival in the capecitabine group was non-inferior to that in the fluorouracil group (76% [95% CI 67–82] vs 67% [58–74]; $p=0\cdot0004$; post-hoc test for superiority $p=0\cdot05$). 3-year disease-free survival was 75% (95% CI 68–81) in the capecitabine group and 67% (59–73) in the fluorouracil group ($p=0\cdot07$). Similar numbers of patients had local recurrences in each group (12 [6%] in the capecitabine group vs 14 [7%] in the fluorouracil group, $p=0\cdot67$), but fewer patients developed distant metastases in the capecitabine group (37 [19%] vs 54 [28%]; $p=0\cdot04$). Diarrhoea was the most common adverse event in both groups (any grade: 104 [53%] patients in the capecitabine group vs 85 [44%] in the fluorouracil group; grade 3–4: 17 [9%] vs four [2%]). Patients in the capecitabine group had more hand-foot skin reactions (62 [31%] any grade, four [2%] grade 3–4 vs three [2%] any grade, no grade 3–4), fatigue (55 [28%] any grade, no grade 3–4 vs 29 [15%], two [1%] grade 3–4), and proctitis (31 [16%] any grade, one [$<1\%$] grade 3–4 vs ten [5%], one [$<1\%$] grade 3–4) than did those in the fluorouracil group, whereas leucopenia was more frequent with fluorouracil than with capecitabine (68 [35%] any grade, 16 [8%] grade 3–4 vs 50 [25%] any grade, three [2%] grade 3–4).

Interpretation Capecitabine could replace fluorouracil in adjuvant or neoadjuvant chemoradiotherapy regimens for patients with locally advanced rectal cancer.

Funding Roche Pharma AG (Grenzach-Wyhlen, Germany).

Introduction

The combination of optimised surgery (total mesorectal excision [TME]) and systematic radiotherapy has substantially improved multimodal treatment of rectal cancer;^{2,3} TME plus short-course radiotherapy yields a 10-year cumulative local recurrence rate of only 5%.³

Fluorouracil in conjunction with neoadjuvant long-term radiotherapy reduced local recurrences in two trials but did not prolong survival.^{4,5} Fluorouracil is often given as adjuvant treatment of rectal cancer, after resection of the primary tumour and neoadjuvant irradiation.⁶ In the European Organisation for Research and Treatment of



Lancet Oncol 2012; 13: 579–88

Published Online

April 13, 2012

DOI:10.1016/S1470-

2045(12)70116-X

See [Comment](#) page 560

Day Treatment Center (TTZ), Interdisciplinary Tumor Center Mannheim (ITM) & III Medical Clinic (Prof R-D Hofheinz MD, D Gencer MD), Clinic for Radiotherapy and Radio-oncology (Prof F Wenz MD), and Clinic and Policlinic for Surgery (Prof S Post MD, Prof P Kienle MD), University Hospital Mannheim, University of Heidelberg, Mannheim, Germany; Clinic for Hematology and Oncology, Caritas Hospital St Theresa, Saarbrücken, Germany (Prof A Matzdorff MD); Clinic for Radio-oncology, University Hospital Tübingen, Tübingen, Germany (S Laechelt MD); Department for Internal Medicine II, University Hospital Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany (Prof J T Hartmann MD); Oncology Practice, Leer, Germany (L Müller MD); Department for Internal Medicine 1, Westpfalz Hospital, Kaiserslautern, Germany (Prof H Link MD); Department for Internal Medicine I, University Hospital Mainz, Mainz, Germany (Prof M Moehler MD); Hospital Magdeburg, Magdeburg, Germany (E Kettner MD); Clinic for Internal Medicine, Stiftungsklinikum Mittelrhein, Koblenz, Germany (E Fritz MD); Oncology Practice, Mannheim, Germany (U Hieber MD); Clinic for Hematology and Oncology, Katholisches Krankenhaus, Hagen, Germany (H W Lindemann MD); Clinic for Internal Medicine, Hospital Aschersleben-Staßfurt, Aschersleben, Germany

(M Grunewald MD); Clinic for Hematology and Oncology, Caritas Hospital, Lebach, Germany (S Kremers MD); Clinic for Hematology and Oncology, Hospital Lippe, Lemgo, Germany (C Constantin MD); Clinic and Policlinic for Radiotherapy, University Hospital Regensburg, Regensburg, Germany (M Hipp MD); Oncology Practice, Groß-Gerau, Germany (Prof G Hartung MD); Department of Biostatistics, German Cancer Research Center (DKFZ) Heidelberg, and STABIL, Zweibrücken, Germany (I Burkholder PhD); and Department for Hematology and Oncology, Clinic for Internal Medicine II, University Hospital Jena, Jena, Germany (Prof A Hochhaus MD)

Correspondence to: Prof Ralf-Dieter Hofheinz, Day Treatment Center (TTZ), Interdisciplinary Tumor Center Mannheim (ITM) & III Medical Clinic, University Hospital Mannheim, University of Heidelberg, 68167 Mannheim, Germany
ralf.hofheinz@umm.de

Cancer (EORTC) 22922 trial,⁵ patients were randomised to bolus fluorouracil or follow-up after resection of the primary tumour and long-term neoadjuvant radiotherapy. 5-year overall survival was 67·2% in the treatment group and 63·2% in controls ($p=0\cdot12$); the hazard ratio (HR) for death in the chemotherapy group was 0·85.⁵ Current evidence favouring the use of fluorouracil in this setting is limited, and national treatment recommendations reflect divergent interpretations of the published data. German guidelines consider adjuvant fluorouracil the standard of care.⁷

Optimisation of local tumour control has meant that distant metastases now represent the most common type of treatment failure in rectal cancer. Modifications of perioperative fluorouracil treatment have been investigated in an attempt to improve overall survival and disease-free survival (DFS); however, neither biomodulation of fluorouracil by folinic acid or levamisole,⁸ nor combination with other cytostatic drugs,^{9,10} have proved superior to bolus fluorouracil, with the exception of infusional fluorouracil given during radiotherapy.⁹

Capecitabine is an oral fluoropyrimidine derivative that was as effective as fluorouracil plus folinic acid for adjuvant treatment of stage III colon cancer.¹¹ It was also non-inferior to infusional fluorouracil in combination with oxaliplatin for first-line treatment of metastatic colorectal cancer.¹² Several phase 1 and 2 trials have investigated capecitabine as part of combinations for perioperative treatment of rectal cancer,¹³ but no randomised trial has compared capecitabine with perioperative fluorouracil in locally advanced disease. Our choice of a non-inferiority trial design was based on the expectation that non-inferiority of capecitabine, given orally on an outpatient basis, would be sufficient to tip the risk-benefit ratio in its favour. Here, we report final results of our phase 3 trial comparing capecitabine with fluorouracil as part of perioperative chemoradiotherapy regimens for locally advanced rectal cancer.

Methods

Study design and patients

This was a two-arm, two-cohort, multicentre, randomised, open-label, non-inferiority, phase 3 trial comparing fluorouracil with capecitabine for perioperative treatment of patients with locally advanced rectal cancer. Patients were recruited from 35 German institutions between March, 2002, and December, 2007. The protocol was approved by the institutional review boards of all participating centres. All participants provided written informed consent.

The study was initiated to compare fluorouracil with capecitabine in patients with locally advanced rectal cancer who had undergone TME or partial mesorectal excision (PME) of the primary tumour (adjuvant cohort). In 2004, the German rectal cancer trial⁶ reported better local control and tolerability with neoadjuvant chemoradiotherapy; therefore, the study protocol was amended

in March, 2005, to include patients with locally advanced rectal cancer receiving preoperative chemoradiotherapy (neoadjuvant cohort). Recruitment to the adjuvant cohort was continued. The trial steering committee endorsed this amendment on the basis that the German rectal cancer trial showed no difference in survival rates or Kaplan-Meier plots of adjuvant versus neoadjuvant groups. Thus, the committee anticipated that the amendment would have no effect on the primary endpoint of the present trial, overall survival.

Eligible patients were 18 years or older and had histologically confirmed adenocarcinoma of the rectum (defined as a distal tumour border <16 cm from the anal verge, measured by rigid rectoscopy), with no evidence of distant metastases (identified by abdominal ultrasound or CT scan and chest radiograph). Patients in the adjuvant cohort had to have undergone R0 resection (ie, leaving no residual tumour) for pT3–4 N_{any} or pT_{any} N_{positive} non-metastatic rectal cancer. TME was mandatory for tumours in the lower two-thirds of the rectum, with PME being permitted for those in the upper third, provided a distal margin of at least 5 cm without coning was observed. Patients in the neoadjuvant cohort had to have a clinical cT3–4 N_{any} or cT_{any} N_{positive} tumour staged by endoscopic ultrasound, provided the lower border of the tumour was 0–16 cm from the anal verge (measured by rigid rectoscopy) and the primary tumour was deemed R0 resectable by TME or PME on the basis of clinical assessment (pelvic CT or MRI were done at the discretion of the local investigators).

Other eligibility criteria were: WHO status 0 or 1; satisfactory liver, renal, and bone-marrow function (leucocytes >3500 cells per μL , platelets >100 000 per μL , haemoglobin >100 g/L); serum bilirubin less than 20 mg/L; and serum creatinine less than 20 mg/L. Exclusion criteria were prior treatment for rectal cancer, prior chemotherapy or immunotherapy, prior pelvic radiotherapy, or a history of other malignant disease within the past 5 years, other than successfully treated basal carcinoma of the skin or carcinoma in situ of the uterine cervix. Patients were also excluded if they were participating in another trial, pregnant, breastfeeding, unwilling to use effective contraception, or had a medical condition or concomitant illness that might impair protocol compliance.

Randomisation and masking

Patients were randomly allocated (by fax request to the Department of Biostatistics, German Cancer Research Center [Heidelberg, Germany]) in a 1:1 ratio to perioperative treatment with capecitabine or fluorouracil, using permuted blocks with stratification by centre and clinical or pathological tumour stage (T3–4 N0 vs T1–2 N_{positive} vs T3–4 N_{positive}). For each stratification group and participating centre, a list was generated by the data centre using S+ software and used to assign treatments. Local investigators were masked to next assignment in

the sequence. The data centre also managed primary and follow-up data using case reports compiled by the participating centres. The study was open-label; patients, treating physicians, and data managers and analysts were not masked to group assignment.

Procedures

Patients randomised to capecitabine were scheduled to receive six cycles of chemotherapy, whereas those in the fluorouracil group received five cycles. Patients in the adjuvant cohort received two cycles of chemotherapy before starting chemoradiotherapy in week 8, thereafter completing chemotherapy with three cycles of capecitabine or two cycles of fluorouracil (figure 1). Patients in the neoadjuvant cohort received chemoradiotherapy for about 6 weeks. TME or PME was done after 4–6 weeks, followed by five cycles of capecitabine or four cycles of fluorouracil (figure 2).

The total irradiation dose of 50.4 Gy was delivered in conventional fractionation (daily fractions of 1.8 Gy over 5–6 weeks, excluding weekends). Three-dimensional conformal techniques with high-energy photons (6–25 MeV) and belly boards were used. The clinical target volume included the entire macroscopic tumour with a minimum margin of 5 cm, the mesorectum (plus 1.0–1.5 cm margin lateral to the pelvic brim), and the

iliac and presacral lymph nodes up to the L5–S1 junction (or L4–L5 junction in the case of extensive lymph-node involvement).

Capecitabine was given twice daily at a cumulative dose of 2500 mg/m² on days 1–14, and repeated on day 22. The total daily dose was divided into two equal amounts and given roughly 12 h apart and within 30 min after a meal, usually breakfast and dinner. Capecitabine was given at a reduced dose of 1650 mg/m² per day throughout radiotherapy, including weekends. Radiotherapy and capecitabine were started on the same day and capecitabine was stopped on the last day of radiotherapy.

Fluorouracil bolus was administered on five consecutive days (days 1–5) and repeated on day 29. Patients in the neoadjuvant cohort received fluorouracil during radiotherapy according to the CAO/ARO/AIO-94 protocol⁶ (ie, 1000 mg/m² per day as a continuous infusion on days 1–5 and 29–33). Patients in the adjuvant cohort received 225 mg/m² per day infusional fluorouracil throughout radiotherapy.⁹

Vital signs, haematology, and biochemistry were monitored weekly during chemoradiotherapy and before each chemotherapy cycle. The protocol stipulated detailed dose-modification criteria according to toxicity, graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.

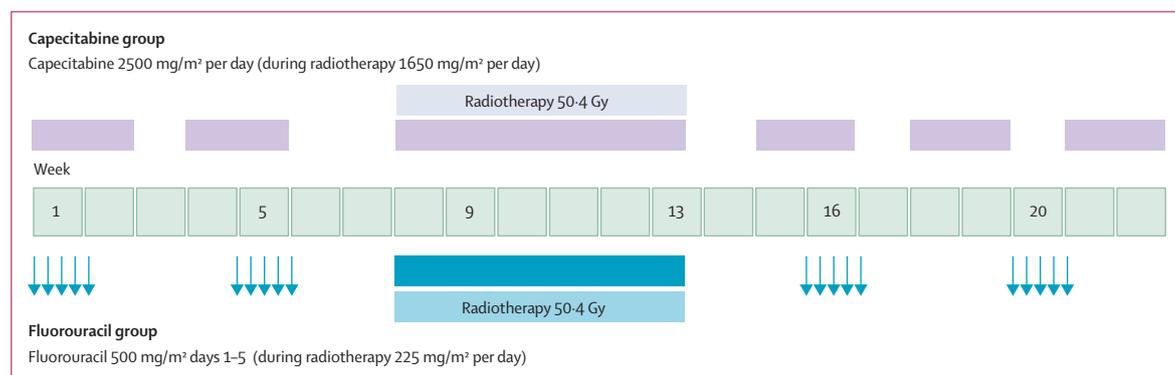


Figure 1: Treatment regimen for the adjuvant cohort

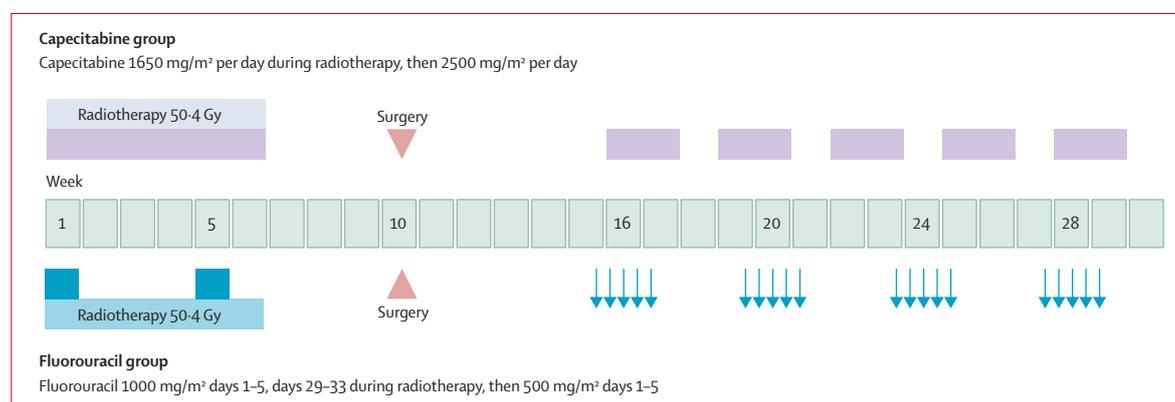


Figure 2: Treatment regimen for the neoadjuvant cohort

TME for tumours of the lower two-thirds of the rectum and PME for the upper third, assuming a 5 cm distal margin without coning, were mandatory for inclusion in the adjuvant cohort and recommended for inclusion in the neoadjuvant cohort, although formal quality assurance in this regard was not implemented. For low-lying tumours, the decision between low anterior resection and abdominoperineal excision was left to the surgeon's discretion.

Baseline assessments were medical history, clinical examination, complete haematology with differential leucocyte count, clinical chemistry including coagulation parameters, tumour markers CEA and CA19-9, electrocardiogram, abdominal ultrasound, and chest radiograph. Additionally, patients in the neoadjuvant cohort underwent complete colonoscopy, rigid rectoscopy, and endorectal ultrasound. Follow-up, done for 5 years after the start of therapy, included clinical examination, haematology, serum biochemistry, tumour markers, and abdominal ultrasound 3 monthly for the first 2 years, and 6 monthly thereafter, in addition to annual chest radiograph. Regular rectoscopy with endorectal ultrasound (months 6, 12, 18, 24, 36, 48, and 60 after removal of the primary tumour) and pelvic CT (months 3, 12, and 24) were done to exclude local recurrence.

Statistical analysis

This trial was designed to test the non-inferiority of 5-year overall survival in the capecitabine versus fluorouracil group. Assuming 57.5% overall survival in the fluorouracil group, a non-inferiority margin of 12.5%, accrual time of 36 months, follow-up of 48 months, 5% drop-out, 5% type I error, and 80% power, sample size calculation using PASS 2000 yielded a total of at least 372 evaluable patients (ie, 186 per group). The assumption of 57.5% overall survival in the fluorouracil group was based on interpolation and extrapolation of survival rates reported by two trials investigating adjuvant fluorouracil-based chemoradiotherapy in rectal cancer.^{8,9} Data were analysed with SAS (version 9.2) and R (version 2.10.1). All analyses were based on all patients with post-randomisation data.

The primary endpoint of overall survival was calculated from the date of randomisation to the date of death. Non-inferiority of 5-year overall survival was tested with a 12.5% margin, using Greenwood's variance estimator for the difference between two survival proportions at 5 years.^{14,15} This was the only confirmatory statistical test. A post-hoc, exploratory, one-sided test of the difference in 5-year overall survival between the groups was used to test superiority of the capecitabine group. Kaplan-Meier

For more on **PASS 2000** software see <http://www.ncss.com>

For more on **SAS software** see <http://www.sas.com>

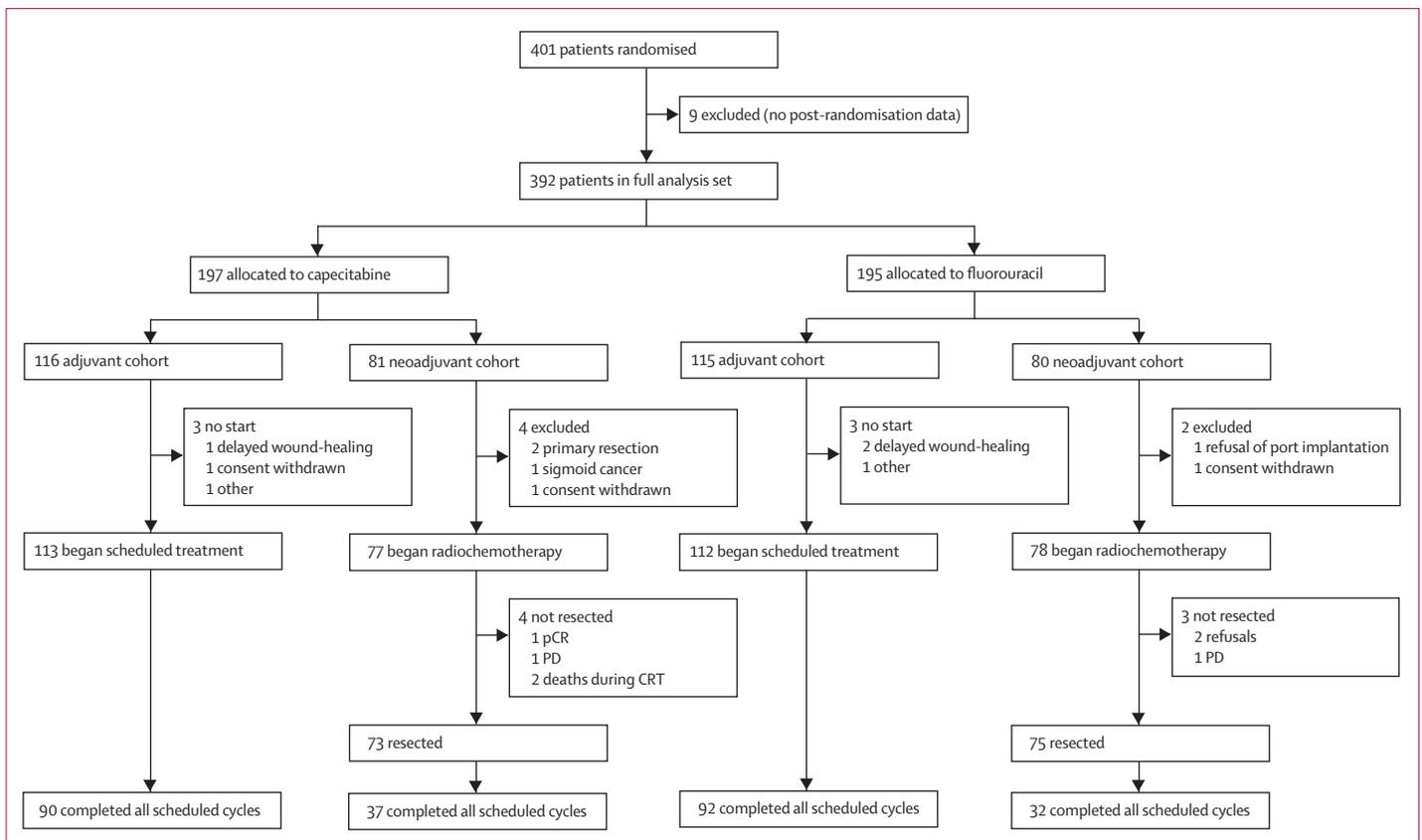


Figure 3: Trial profile
pCR=pathological complete remission. PD=progressive disease. CRT=chemoradiotherapy.

survival estimates were compared using the log-rank test. Cox proportional HRs were calculated for different subgroups (cohort, sex, age, stratum, WHO status, type of surgery, and resection status). The assumption of proportional hazards was assessed using Schoenfeld residuals and by testing a time-dependent covariate defined as interaction between treatment group and log survival time.

The secondary endpoint of DFS was calculated from the date of randomisation to the date of disease recurrence (metastasis or local recurrence), development of a second primary cancer (including non-colorectal carcinoma), or death from any cause, whichever occurred first. DFS was analysed using censored failure times with the Kaplan-Meier method, with exploratory two-sided tests of the difference in 3-year DFS between groups. Additionally, Cox proportional HR for treatment difference in DFS was calculated for the overall population. Other secondary endpoints were local recurrence (pelvic or perineal tumour), distant metastases, and treatment toxicity.

Proportions were compared using a χ^2 test, and continuous variables were compared using Wilcoxon's rank-sum test. A p value of 0.05 or lower was considered significant. All statistical tests for secondary endpoints, particularly those concerning safety, were interpreted descriptively and exploratorily and no formal statistical conclusions were drawn. No imputation methods for missing values were applied. A linear association over the ordered categories ypT0 versus ypT1–2 versus ypT3–4 was tested for patients in the neoadjuvant cohort, using an exact Mantel-Haenszel χ^2 test.

This trial is registered with ClinicalTrials.gov, number NCT01500993.

Role of the funding source

Roche Pharma AG provided capecitabine and a research grant for the trial, but had no role in the study design, data collection, analysis, or interpretation, writing of this report, or the decision to submit for publication. R-DH, FW, IB, DG, and AH had access to the raw data. The corresponding author had full access to all study data and final responsibility for the decision to submit for publication.

Results

401 patients were randomised between March 20, 2002, and Dec 10, 2007 (figure 3). Nine patients were excluded because no post-randomisation data were available for analysis. Thus, the full analysis set comprised 392 patients; 197 in the capecitabine group and 195 in the fluorouracil group (231 in the adjuvant cohort, 161 in the neoadjuvant cohort). Baseline patient and tumour characteristics were well balanced between the two groups (table 1). Men accounted for two-thirds of patients in both groups. Most patients had a cT3 or pT3 tumour, with a slight predominance of T3–4 stages in the

capecitabine group along with somewhat fewer positive nodal stages.

Follow-up was continued until February, 2011. Median follow-up was 52 months (IQR 41–72) and was similar in both groups (51 months [41–75] capecitabine *vs* 53 months [42–73] fluorouracil). By the time of the analysis, 93 patients had died (38 in the capecitabine group and 55 in the fluorouracil group; table 2); 63 of 93 deaths (68%) were due to the underlying cancer (26 [68%] of 38 in the capecitabine group *vs* 37 [67%] of 55 in the fluorouracil group; $p=0.91$). However, there were significantly fewer deaths in the capecitabine group (38 [19%] of 197 *vs* 55 [28%] of 195; $p=0.04$), resulting in an absolute reduction of 6% in the risk of disease-related death in the capecitabine group.

	Capecitabine (n=197)	Fluorouracil (n=195)
Age (years)	65 (30–85)	64 (33–86)
Sex		
Male	129 (65%)	131 (67%)
Female	68 (35%)	64 (33%)
WHO status		
0	120 (61%)	96 (49%)
1	60 (30%)	78 (40%)
2	3 (2%)	1 (<1%)
Missing data	14 (7%)	20 (10%)
Cohort		
Adjuvant	116 (59%)	115 (59%)
Neoadjuvant	81 (41%)	80 (41%)
Tumour category*		
T1 or T2	29 (15%)	36 (18%)
T3	150 (76%)	140 (72%)
T4	15 (8%)	14 (7%)
Missing data	3 (2%)	5 (3%)
Nodal category*		
Node negative	78 (40%)	69 (35%)
Node positive	112 (57%)	120 (62%)
Missing data	7 (4%)	6 (3%)

Data are n (%) or median (range). *Clinical or pathological category.

Table 1: Baseline characteristics of the study population

	Capecitabine (n=197)	Fluorouracil (n=195)	p value*
Site of recurrence			
Local	12 (6%)	14 (7%)	0.67*
Distant	37 (19%)	54 (28%)	0.04*
Deaths			
Total	38 (19%)	55 (28%)	0.04*
Disease-related	26 (13%)	37 (19%)	
Other causes	12 (6%)	15 (8%)	
Unknown	0	3 (2%)	

Data are cumulative number of events (%). * χ^2 test.

Table 2: Disease-related events

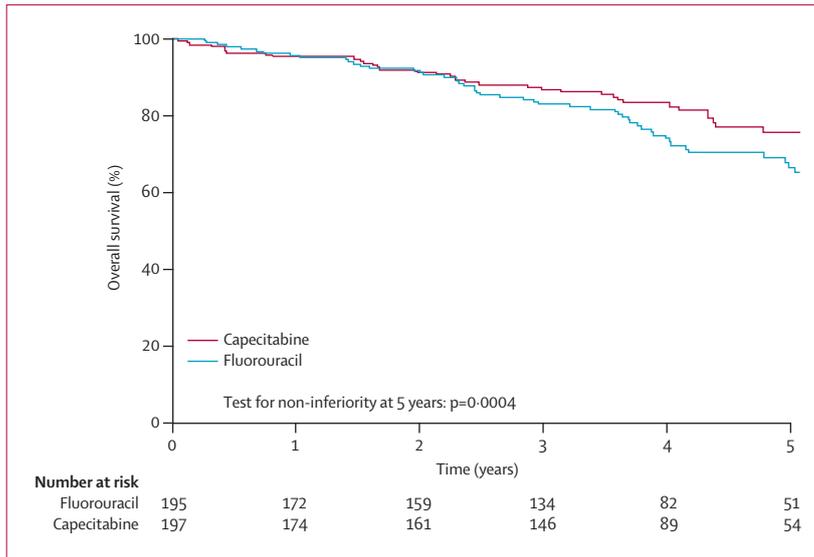


Figure 4: Overall survival

5-year overall survival in the capecitabine group was non-inferior to that in the fluorouracil group (76% [95% CI 67–82] in the capecitabine group vs 67% [58–74] in the fluorouracil group, non-inferiority $p=0.0004$; figure 4; hazard ratio [HR] for fluorouracil vs capecitabine 1.5 [95% CI 1.00–2.28]). An exploratory, post-hoc test for superiority in 5-year overall survival was in favour of capecitabine ($p=0.05$). Better 5-year overall survival with capecitabine than with fluorouracil was noted in both the adjuvant (81% [95% CI 71–87] vs 71% [60–79]) and the neoadjuvant cohort (66% [46–81]) vs 61% [46–73]).

Capecitabine was associated with improved survival in all subgroups that included a sufficiently large number of patients (figure 5). For example, an HR of 1.70 (1.08–2.68) was seen in the T3–4N+ subgroup (310 patients), suggesting that these patients, who have a higher risk of relapse, derived substantial benefit from capecitabine. The effect of capecitabine relative to fluorouracil was noted for both cohorts, although it was slightly smaller in the neoadjuvant cohort than in the adjuvant cohort (HR 1.28 [95% CI 0.69–2.37] vs 1.62 [0.92–2.86] in the adjuvant cohort). This difference in treatment effect between cohorts was not significant. Comparison using a Cox model adjusted for treatment and cohort revealed an HR of 1.5 (0.98–2.24), showing that treatment cohort did not affect analysis of the primary endpoint.

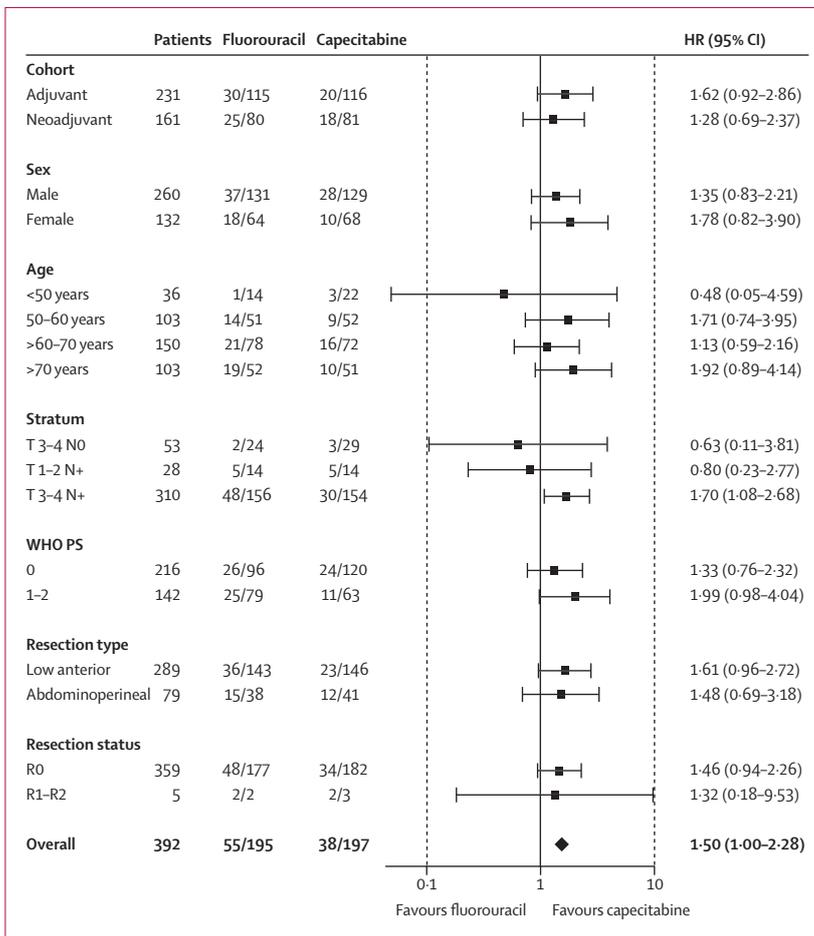


Figure 5: Forest plot analysis of overall survival in subgroups (fluorouracil vs capecitabine)

The number of patients with a local recurrence was similar between groups (12 [6%] in the capecitabine group vs 14 [7%] in the fluorouracil group; $p=0.67$), but fewer patients in the capecitabine group had distant metastasis than did those in the fluorouracil group (37 [19%] vs 54 [28%]; $p=0.04$; table 2). DFS was better in the capecitabine group than in the fluorouracil group (HR 1.4 [95% CI 1.02–2.02]; log-rank $p=0.035$; figure 6). 3-year DFS was higher in the capecitabine group than in the fluorouracil group (75% [95% CI 68–81] vs 67% [59–73]; $p=0.07$; table 3). Better 3-year DFS with capecitabine than with fluorouracil was noted in both the adjuvant (78% [69–85] vs 69% [59–77]) and neoadjuvant cohorts (71% [60–80] vs 63% [51–73]).

In the adjuvant cohort, 90 patients (78%) in the capecitabine group and 92 (80%) in the fluorouracil group completed their scheduled cycles (table 4). Although a substantial proportion of patients in the neoadjuvant cohort did not continue chemotherapy after resection of the primary tumour, a similar proportion completed chemotherapy in both groups: 37 (46%) in the capecitabine group versus 32 (40%) in the fluorouracil group (table 4). Of the patients in the neoadjuvant cohort starting postoperative treatment, 37 (74%) of 50 patients in the capecitabine group and 32 (70%) of 46 patients in the fluorouracil group completed all postoperative scheduled cycles.

Significant differences between groups in the number of patients experiencing a toxic effect were noted for fatigue, proctitis, and hand-foot skin reactions, which

were more frequent in the capecitabine group, and leucopenia, which was more frequent in the fluorouracil group (table 5). Diarrhoea was the most common adverse event (table 5). Rates of diarrhoea during chemotherapy were almost identical between groups (all-grade diarrhoea: 47 [24%] of 197 patients in the capecitabine group vs 43 [22%] of 195 in the fluorouracil group; $p=0.67$), but were significantly higher in the capecitabine group during radiochemotherapy (88 [45%] vs 62 [32%]; $p=0.009$).

Hand-foot skin reactions were reported by 62 (31%) patients receiving capecitabine, but by only three (2%) of those receiving fluorouracil. In a post-hoc analysis, patients in the capecitabine group who developed any-grade hand-foot skin reactions had better DFS and overall survival than did those who did not develop hand-foot skin reactions (3-year DFS: 83% [95% CI 71–91] vs 71% [63–79], $p=0.03$; 5-year overall survival: 91% [95% CI 81–96] vs 68% [57–77], $p=0.0001$). Similar differences in survival were noted when comparing patients in the capecitabine group who developed hand-foot skin reactions with the overall study population (for 3-year DFS, $p=0.004$ and for 5-year overall survival, $p<0.0001$ vs the remaining population [$n=330$]).

148 patients in the neoadjuvant cohort underwent surgery: 73 (90%) of 81 patients in the capecitabine group and 75 (94%) of 80 patients in the fluorouracil group. Unresectable tumour spread made surgery impossible in one patient in the fluorouracil group; one patient in the capecitabine group had local excision only because of major tumour remission after neoadjuvant therapy (figure 3). The mean pretreatment tumour distance from dentate line to lower tumour margin was 5 cm (SD 4) in the capecitabine group and 6 cm (SD 4) in the fluorouracil group ($p=0.04$). Resection type and status did not differ significantly between capecitabine and fluorouracil groups (low-anterior resection in 53 [73%] of 73 patients in the capecitabine group vs 58 [78%] of 74 in the fluorouracil group, $p=0.42$; R0 resection in 69 [96%] of 72 [excluding the patient who underwent local excision] in the capecitabine group vs 68 [92%] of 74 in the fluorouracil group, $p=0.32$).

Pathological complete remission (pCR; ypT0N0) was more frequent in the capecitabine group, being achieved by ten (14%) of 73 patients in the capecitabine group versus four (5%) of 74 in the fluorouracil group ($p=0.09$). More patients in the capecitabine group had a ypT0–2 tumour (40 [55%] of 73 vs 29 [39%] of 74; $p=0.06$). A two-sided exact Mantel-Haenszel test for difference in the ordered categories ypT0 versus ypT1–2 versus ypT3–4 showed a significant association for lower T categories in the capecitabine group ($p=0.03$), which suggests improved tumour shrinkage using capecitabine. Information on pretreatment clinical nodal staging was available for 150 patients. About half the patients in each group had a clinically staged node-positive primary tumour (36 [48%] of 75 patients in the capecitabine group

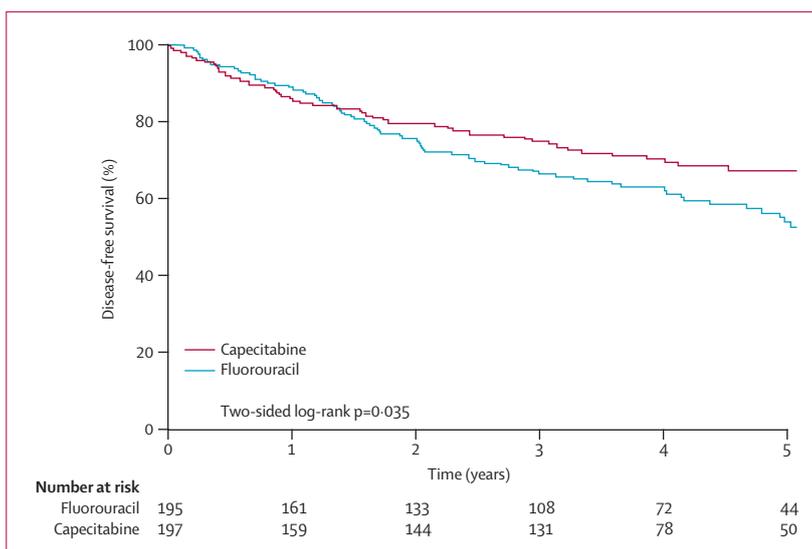


Figure 6: Disease-free survival

	Capecitabine (n=197)	Fluorouracil (n=195)
Disease-free survival, % (95% CI)		
3 year	75% (68–81)	67% (59–73)
5 year	68% (60–74)	54% (45–62)
Overall survival, % (95% CI)		
3 year	87% (81–91)	83% (77–88)
5 year	76% (67–82)	67% (58–74)
7 year	71% (60–79)	58% (47–67)

Table 3: Kaplan-Meier survival estimates

	Capecitabine	Fluorouracil
Adjuvant cohort*		
1	113 (97%)	112 (97%)
2	110 (95%)	106 (92%)
3	104 (90%)	101 (88%)
4	100 (86%)	96 (84%)
5	98 (85%)	92 (80%)
6	90 (78%)	..
Neoadjuvant cohort†		
1	74 (91%)	76 (95%)
2	50 (62%)	46 (58%)
3	46 (57%)	38 (48%)
4	42 (52%)	35 (44%)
5	40 (49%)	32 (40%)
6	37 (46%)	..

Data are n (%). *n=116 for capecitabine, n=115 for fluorouracil. †n=81 for capecitabine, n=80 for fluorouracil.

Table 4: Patients receiving scheduled treatment, per cycle

vs 39 [52%] of 75 in the fluorouracil group; $p=0.70$). By contrast, pathological staging after neoadjuvant chemoradiotherapy revealed more node-negative tumours in the capecitabine group than in the fluorouracil group

	Capecitabine (n=197)			Fluorouracil (n=195)			p value*
	Grade 1-2	Grade 3-4	Total†	Grade 1-2	Grade 3-4	Total†	
Laboratory							
Lowered haemoglobin	58	0	62	49	2	52	0.29
Lowered leucocytes	47	3	50	50	16	68	0.04
Lowered platelets	23	0	23	29	1	32	0.18
Raised creatinine	5	0	5	2	0	2	0.26
Raised bilirubin	6	1	8	1	1	2	0.06
Gastrointestinal							
Nausea	33	2	36	30	0	32	0.63
Vomiting	11	1	14	8	1	9	0.30
Diarrhoea	83	17	104	76	4	85	0.07
Mucositis	11	1	12	15	2	17	0.32
Stomatitis	8	0	8	11	0	12	0.35
Abdominal pain	19	1	23	11	0	14	0.13
Proctitis	26	1	31	9	1	10	<0.001
Other							
Fatigue	50	0	55	27	2	29	0.002
Anorexia	13	0	13	5	1	6	0.10
Alopecia	4	0	4	11	0	11	0.06
Hand-foot skin reaction	56	4	62	3	0	3	<0.001
Radiation dermatitis	22	2	29	32	1	35	0.39

Data are number of patients or p value. *Derived from χ^2 test comparing total events between treatment groups.
†CTC grade was missing in some patients.

Table 5: Toxic effects per treatment group, according to National Cancer Institute Common Toxicity Criteria (CTC) version 2.0

(51 [71%] of 72 patients in the capecitabine group vs 42 [57%] of 74 in the fluorouracil group; $p=0.08$).

Discussion

Six cycles of capecitabine were non-inferior to five cycles of fluorouracil with regard to 5-year overall survival in patients receiving neoadjuvant or adjuvant chemoradiotherapy for locally advanced rectal cancer. DFS was higher in the capecitabine group than in the fluorouracil group because fewer distant metastases occurred with capecitabine than with fluorouracil. A post-hoc exploratory test of superiority in 5-year overall survival showed a clinically meaningful survival benefit in favour of capecitabine. This result was substantiated by the Cox proportional HR for the overall population, which favoured capecitabine and had a lower 95% CI boundary of 1.00. In the neoadjuvant cohort, more patients who received capecitabine achieved a pathological complete response or ypT0–2 than did those in the fluorouracil group; there was also evidence of greater nodal downstaging for patients who received capecitabine than with fluorouracil. With the exception of a higher rate of gastrointestinal toxicity during radiotherapy and higher rates of hand-foot skin reactions, capecitabine was generally as well tolerated as fluorouracil.

The present study began as an adjuvant trial in 2002, and was amended to include a neoadjuvant

cohort in 2005, after publication of the German rectal cancer study.⁶ The German trial showed a significant reduction in local recurrence and improved tolerability with neoadjuvant versus adjuvant chemoradiotherapy, although there was no difference in survival. Our steering committee concluded that it was appropriate to add a neoadjuvant cohort to the present study, since there was no indication that such patients would fare better with regard to 5-year overall survival. In our study, an overall benefit in 5-year overall survival and 3-year DFS was seen for patients who received capecitabine in both adjuvant and neoadjuvant cohorts. Statistical analyses were done to assess the treatment effect separately for each cohort. The HR for treatment effect (fluorouracil vs capecitabine) was similar between cohorts, although slightly smaller in the neoadjuvant cohort. Furthermore, the cohort-adjusted overall HR for treatment effect differed only marginally from the unadjusted overall treatment effect. In summary, Cox analyses showed that overall conclusions regarding the primary endpoint of 5-year overall survival were not affected by the cohort effect, and that a treatment-cohort interaction can be excluded.

Although this study was designed as a non-inferiority trial, the results indicate improved efficacy with capecitabine. These improvements are not explained by better treatment adherence: the same proportion of patients completed their scheduled cycles in both treatment groups and in both cohorts. Nor can improved efficacy be explained by improved local control; local recurrence rates were similar in both treatment groups, suggesting good-quality surgery and radiotherapy, although no formal quality control was done. The capecitabine group showed a significant reduction in distant metastases and improved DFS, suggesting greater systemic efficacy than with bolus fluorouracil. The X-ACT study^{11,16} reached a similar conclusion when comparing capecitabine with bolus fluorouracil plus folinic acid for adjuvant treatment of stage III colon cancer. The study achieved its primary aim of showing at least equivalence in DFS between capecitabine and fluorouracil plus folinic acid. Superiority analysis showed a non-significant improvement in 3-year DFS with capecitabine (64% vs 61%; $p=0.12$).¹¹ Long-term follow-up over a median of 6.9 years and preplanned multivariate analyses showed that capecitabine significantly improved DFS ($p=0.02$) and overall survival ($p=0.02$) versus fluorouracil plus folinic acid.¹⁶ Thus, the present study and the X-ACT trial support use of capecitabine over bolus fluorouracil in the adjuvant treatment of colorectal cancer.

Retrospective analyses of phase 2 studies where capecitabine was given in combination with radiotherapy have shown cumulative pCR rates that are similar to infusional fluorouracil. Sanghera and colleagues¹⁷ found similar pCR rates with capecitabine (17%) and infusional fluorouracil (20%) in a meta-analysis of 71 trials with a total of 4732 patients. In the present trial, we used the German standard infusional fluorouracil regimen in

the neoadjuvant cohort: 120 h continuous infusion of fluorouracil (1000 mg/m² per day) in weeks 1 and 5 of chemoradiotherapy. Capecitabine improved T downstaging and pCR rate (14% vs 5% with fluorouracil). National Surgical Adjuvant Breast and Bowel Project (NSABP) trial R-04¹⁸ compared protracted venous infusional fluorouracil (225 mg/m² per day) with capecitabine at the same dose as in the present study, for preoperative treatment of rectal cancer. Addition of oxaliplatin to either regimen was investigated using a two-by-two factorial design. Preliminary data showed a slightly better pCR rate with capecitabine with or without oxaliplatin, than with fluorouracil with or without oxaliplatin (22% [95% CI 19–26] vs 19% [16–22]; *p*=0·12). The NSABP R-04 study has not yet presented data on pCR rates with capecitabine or fluorouracil alone. The study had similar rates of sphincter-sparing surgery in both arms, comparable to the neoadjuvant cohort of the present trial; it also noted similar rates of any surgical complication with capecitabine versus fluorouracil (37% vs 35%). Capecitabine did not increase postoperative morbidity. In the present trial, we noted higher rates of proctitis and diarrhoea with capecitabine during radiotherapy, the latter increasing by 13% compared with fluorouracil. Similarly, patients who received capecitabine in NSABP R-04 had slightly more symptoms (particularly diarrhoea) than those who received fluorouracil, as measured with the fluoropyrimidine-specific symptom checklist.¹⁹ Nevertheless, using the Functional Assessment of Cancer Therapy–Colorectal (FACT-C) trial-outcome index, quality of life was identical between groups in NSABP R-04, and capecitabine provided greater convenience of care.¹⁹

The general level of toxicity observed in the present trial can be regarded as low to moderate in both treatment groups. As expected, toxicity patterns differed. Capecitabine caused higher gastrointestinal toxicity during radiotherapy, but the rate of diarrhoea during cycles with chemotherapy alone did not differ between groups. Hand-foot skin reactions and fatigue were more frequent with capecitabine, and leucopenia was more frequent with fluorouracil. A third of patients receiving capecitabine had hand-foot skin reactions. In a post-hoc analysis, patients in the capecitabine group who developed any-grade hand-foot skin reactions had significantly better 3-year DFS and 5-year overall survival than capecitabine patients with no hand-foot skin reactions, or the remaining study population. Nonetheless, 3-year DFS for patients who received capecitabine but did not develop hand-foot skin reactions was much the same as for those who received fluorouracil (71% [95% CI 63–79] vs 67% [59–73]). In this respect, hand-foot skin reactions might be regarded as a positive pharmacodynamic prognostic marker. The same effect was reported in the X-ACT trial (panel),¹⁶ and in a randomised phase 2 study using capecitabine as part of combination chemotherapy in patients with metastatic colorectal

Panel: Research in context

Systematic review

Until the early 2000s, adjuvant chemoradiotherapy was considered standard of care for stage II–III rectal cancer in Germany and other European countries. Several trials and strategies, including biomodulation of fluorouracil, prolongation of adjuvant treatment, and addition of drugs such as semustine, did not improve on results with fluorouracil treatment.^{8,9} At the time the present trial was designed, capecitabine was being investigated as an alternative to infusional fluorouracil in combination regimens in metastatic colorectal cancer.¹² No evidence existed as to whether capecitabine could substitute for fluorouracil in the perioperative treatment of rectal cancer. No systematic review had been done before the start of the present trial, although the steering committee was unaware of other studies on the same question. After our study began, the German rectal cancer study⁶ showed that neoadjuvant (vs adjuvant) chemoradiotherapy improved local relapse rates and tolerability, with no difference in overall survival. Our steering committee decided to include a neoadjuvant treatment cohort, in the absence of evidence that the timing of chemoradiotherapy affected overall survival, our primary endpoint.

Interpretation

Our data are similar to those from the X-ACT study,^{11,16} which compared capecitabine with bolus fluorouracil in stage III colon cancer. X-ACT also showed the non-inferiority of capecitabine, and both trials showed improvement in disease-free survival in the capecitabine group. In the present trial, an association with better disease-free and overall survival with capecitabine was noted for both cohorts, suggesting the absence of a treatment-cohort interaction. Similarly, the NSABP-R04 trial^{18,19} recently showed that capecitabine can replace infusional fluorouracil in neoadjuvant chemoradiotherapy for rectal cancer. Our findings reinforce the evidence that capecitabine can replace fluorouracil in perioperative and palliative treatment of colorectal cancer. Therefore, clinicians might consider using capecitabine instead of fluorouracil in adjuvant or neoadjuvant chemoradiotherapy for patients with locally advanced rectal cancer.

cancer.²⁰ Assessing individual dose optimisation for capecitabine according to the presence or absence of hand-foot skin reactions might be a worthwhile strategy for future studies.

Current clinical research focuses on improving fluorouracil or capecitabine-based neoadjuvant^{18,21,22} or perioperative treatment²³ by adding oxaliplatin, as in the ongoing CAO/ARO/AIO-04²³ and PETACC-6 (NCT00766155) trials, which have both completed accrual. Until the final results of both studies are reported, capecitabine can be regarded as an effective, well tolerated, and convenient alternative to fluorouracil in patients undergoing adjuvant or neoadjuvant chemoradiotherapy for locally advanced rectal cancer.

Contributors

R-DH, FW, SP, GH, and AH designed the study. R-DH, FW, SP, AM, SL, JTH, LM, HL, MM, EK, EF, UH, HWL, MG, SK, CC, MH, GH, DG, PK, and AH were responsible for treatment of study patients and data collection. R-DH, FW, IB, and AH did the data analysis and interpretation, and wrote the report. All authors approved the final version.

Conflicts of interest

R-DH has consulted for and received honoraria and research grants from Roche Pharma AG, and has received honoraria from Chugai Pharma. AM has consulted for and received honoraria and travel grants from Roche Pharma AG. JTH and MM have received honoraria from

Roche Pharma AG. UH has received honoraria from Chugai Pharma and Roche Pharma AG. AH has consulted for Ariad, Bristol-Myers Squibb, Novartis, Merck Sharp & Dohme, and Pfizer, and has received research grants from Ariad, Bristol-Myers Squibb, Novartis, and Roche Pharma AG. All other authors declared no conflicts of interest.

Acknowledgments

We thank all investigators and study coordinators. We also thank Lutz Edler, Annette Kopp-Schneider, and Lothar Pilz (Department of Biostatistics at German Cancer Research Center, Heidelberg, Germany), and Petra Mura, Renate Kapaun, and Tanja Groh (trial unit at the Third Department of Internal Medicine, Mannheim University Hospital, University of Heidelberg, Mannheim, Germany).

References

- Martling A, Holm T, Rutqvist LE, et al. Impact of a surgical training programme on rectal cancer outcomes in Stockholm. *Br J Surg* 2005; **92**: 225–29.
- Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; **373**: 811–20.
- van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12**: 575–82.
- Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFC9203. *J Clin Oncol* 2006; **24**: 4620–25.
- Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**: 1114–23.
- Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**: 1731–40.
- Schmiegel W, Reinacher-Schick A, Arnold D. Update S3-guideline colorectal cancer 2008. *Z Gastroenterol* 2008; **46**: 799–840 (in German).
- Tepper J, O'Connell MJ, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control—final report of intergroup 0114. *J Clin Oncol* 2002; **20**: 1744–50.
- O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994; **331**: 502–07.
- Kalofonos HP, Bamias A, Koutras A, et al. A randomised phase III trial of adjuvant radio-chemotherapy comparing irinotecan, 5FU and leucovorin to 5FU and leucovorin in patients with rectal cancer: a Hellenic Cooperative Oncology Group Study. *Eur J Cancer* 2008; **44**: 1693–700.
- Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005; **352**: 2696–704.
- Cassidy J, Clarke S, Díaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 2006–12.
- Glynn-Jones R, Dunst J, Sebag-Montefiore D, et al. The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: how successful have we been? *Ann Oncol* 2006; **17**: 361–71.
- Tunes da Silva G, Logan BR, Klein JP. Methods for equivalence and non-inferiority testing. *Biol Blood Marrow Transplant* 2009; **15** (suppl 1): 120–27.
- Machin D, Gardner MJ. Calculating confidence intervals for survival time analyses. *BMJ* 1988; **296**: 1369–71.
- Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine versus 5 fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. *Ann Oncol* published online Sept 6, 2011. DOI:10.1093/annonc/mdr366.
- Sanghera P, Wong DW, McConkey CC, Geh JI, Hartley A. Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. *Clin Oncol (R Coll Radiol)* 2008; **20**: 176–83.
- Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. *Proc Am Soc Clin Oncol* 2011; **29** (suppl): abstr 3503.
- Yothers G, Ganz PA, Lopa SH, Ko CY, Wickerham DL, Wolmark N. Patient-reported outcomes (PROs) comparison of 5 FU and capecitabine (cape) with concurrent radiotherapy (RT) for neoadjuvant treatment of rectal cancer: results of NSABP R-04. *Proc Am Soc Clin Oncol* 2012; **30** (suppl 4): abstr 391.
- Stintzing S, Fischer von Weikersthal L, Vehling-Kaiser U, et al. Correlation of capecitabine-induced skin toxicity with treatment efficacy in patients with metastatic colorectal cancer: results from the German AIO KKR-0104 trial. *Br J Cancer* 2011; **105**: 206–11.
- Gérard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; **28**: 1638–44.
- Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol* 2011; **29**: 2773–80.
- Roedel C, Becker H, Fietkau R, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: first results of the German CAO/ARO/AIO-04 randomized phase III trial. *Proc Am Soc Clin Oncol* 2011; **29** (suppl): LBA3505.