

ORIGINAL ARTICLE

Capecitabine as Adjuvant Treatment for Stage III Colon Cancer

Chris Twelves, M.D., Alfred Wong, M.D., Marek P. Nowacki, M.D., Markus Abt, Ph.D., Howard Burris III, M.D., Alfredo Carrato, M.D., Jim Cassidy, M.D., Andrés Cervantes, M.D., Jan Fagerberg, M.D., Ph.D., Vassilis Georgoulas, M.D., Fares Hussein, M.D., Duncan Jodrell, M.D., Piotr Koralewski, M.D., Hendrik Kröning, M.D., Jean Maroun, M.D., Norbert Marschner, M.D., Joseph McKendrick, M.D., Marek Pawlicki, M.D., Riccardo Rosso, M.D., Johannes Schüller, M.D., Jean-François Seitz, M.D., Borut Stabuc, M.D., Ph.D., Jerzy Tujakowski, M.D., Guy Van Hazel, M.D., Jerzy Zaluski, M.D., and Werner Scheithauer, M.D.*

From the University of Leeds and Bradford NHS Hospitals' Trust, Leeds, and Cancer Research U.K., Department of Medical Oncology, University of Glasgow, Glasgow, United Kingdom (C.T.); Tom Baker Cancer Centre, Calgary, Alta., Canada (A.W.); Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland (M.P.N.); Hoffmann-La Roche, Basel, Switzerland (M.A., J.F.); Sarah Cannon Cancer Center, Nashville (H.B.); Hospital General de Elche, Elche, Alicante, Spain (A. Carrato); Cancer Research U.K., Department of Medical Oncology, University of Glasgow, Glasgow, and Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen — both in the United Kingdom (J.C.); Hospital Clínico, Valencia, Spain (A. Cervantes); University Hospital of Crete, Heraklion, Greece (V.G.); Hôpital Pasteur, Colmar, France (F.H.); University of Edinburgh, Edinburgh, United Kingdom (D.J.); Rydygier Memorial Hospital, Krakow–Nowa Huta, Poland (P.K.); Städtisches Klinikum Magdeburg, Magdeburg, Germany (H.K.); Ottawa Regional Cancer Centre, Ottawa (J. Maroun); Outpatient Cancer Center, Freiburg, Germany (N.M.); Box Hill Hospital, Melbourne, Australia (J. McKendrick); Cancer Institute, Krakow, Poland (M.P.); Instituto Nazionale per la Ricerca sul Cancro, Genoa, Italy (R.R.); Krankenanstalt Rudolfstiftung, Vienna (J.S.); Hôpital La Timone, Marseille, France (J.-F.S.); Klinicni Center Ljubljana, Ljubljana, Slovenia (B.S.); Regional Center of Oncology, Bydgoszcz, Poland (J.T.); Perth Oncology, Mount Hospital, West Perth, Australia (G.V.H.); Great Poland Cancer Center, Poznan, Poland (J.Z.); and Allgemeines Krankenhaus-Universität Kliniken Wien, Vienna (W.S.). Address reprint requests to Dr. Twelves at the Tom Connors Cancer Research Centre, University of Bradford, Richmond Road, Bradford BD7 1DP, United Kingdom, or at c.twelves@bradford.ac.uk.

*Other investigators in the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial are listed in the Appendix.

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ABSTRACT

BACKGROUND

Intravenous bolus fluorouracil plus leucovorin is the standard adjuvant treatment for colon cancer. The oral fluoropyrimidine capecitabine is an established alternative to bolus fluorouracil plus leucovorin as first-line treatment for metastatic colorectal cancer. We evaluated capecitabine in the adjuvant setting.

METHODS

We randomly assigned a total of 1987 patients with resected stage III colon cancer to receive either oral capecitabine (1004 patients) or bolus fluorouracil plus leucovorin (Mayo Clinic regimen; 983 patients) over a period of 24 weeks. The primary efficacy end point was at least equivalence in disease-free survival; the primary safety end point was the incidence of grade 3 or 4 toxic effects due to fluoropyrimidines.

RESULTS

Disease-free survival in the capecitabine group was at least equivalent to that in the fluorouracil-plus-leucovorin group (in the intention-to-treat analysis, $P < 0.001$ for the comparison of the upper limit of the hazard ratio with the noninferiority margin of 1.20). Capecitabine improved relapse-free survival (hazard ratio, 0.86; 95 percent confidence interval, 0.74 to 0.99; $P = 0.04$) and was associated with significantly fewer adverse events than fluorouracil plus leucovorin ($P < 0.001$).

CONCLUSIONS

Oral capecitabine is an effective alternative to intravenous fluorouracil plus leucovorin in the adjuvant treatment of colon cancer.

ALMOST 1 MILLION PATIENTS RECEIVE A diagnosis of colorectal cancer yearly, and half a million deaths from this neoplasm occur annually worldwide.¹ Each year, approximately 230,000 patients with colon cancer are eligible for adjuvant chemotherapy.¹⁻³ The benefits of fluorouracil-based adjuvant chemotherapy in reducing the risk of relapse and prolonging survival in patients with resected colon cancer are well established, particularly in stage III disease.⁴⁻⁶ Survival advantages were demonstrated with bolus intravenous fluorouracil plus leucovorin administered according to the Mayo Clinic regimen (five days, monthly, for six months) or the Roswell Park regimen (weekly bolus, six of every eight weeks, for eight months).^{5,7-10} The choice between these regimens involves a decision about toxic effects: stomatitis and neutropenia with the Mayo Clinic regimen or diarrhea with the Roswell Park regimen. Infused fluorouracil regimens have also been evaluated, but they have no greater efficacy than bolus fluorouracil plus leucovorin in the adjuvant setting.¹¹⁻¹³ For this reason, six to eight months of treatment with bolus fluorouracil plus leucovorin has been the standard of care worldwide as adjuvant treatment of colon cancer since the 1990s.¹⁴

There are, however, discrepancies between consensus recommendations and adjuvant treatment in the community.^{10,15-17} More effective, better tolerated, and more convenient chemotherapy is required, especially for patients older than 65 years,¹⁸ who are less likely to receive rigorous chemotherapy.^{16,17} Moreover, most patients (84 to 89 percent) with cancer would prefer oral chemotherapy, provided efficacy is not compromised.^{19,20}

The oral fluoropyrimidine capecitabine (Xeloda, Hoffmann-La Roche) generates fluorouracil preferentially in tumor tissue, by way of a three-step enzymatic cascade.²¹ The final stage of conversion to fluorouracil is catalyzed by thymidine phosphorylase, which is appreciably more active in tumor than in healthy tissue.^{21,22} As first-line treatment for metastatic colorectal cancer, capecitabine is an established alternative to the combination of fluorouracil and leucovorin. It achieved response rates superior to those achieved with the Mayo Clinic regimen (26 percent vs. 17 percent), with equivalent progression-free survival and overall survival.²³ Capecitabine was also associated with fewer adverse effects than the Mayo Clinic regimen²⁴ and reduced the use of medical resources.²⁵

These data provided the rationale for a phase 3

trial (Xeloda in Adjuvant Colon Cancer Therapy [X-ACT]) to compare capecitabine and the Mayo Clinic fluorouracil-plus-leucovorin regimen as adjuvant treatment in resected stage III colon cancer. The primary objective was to demonstrate that capecitabine was at least equivalent to fluorouracil plus leucovorin in terms of disease-free survival. We report here planned analyses of the primary efficacy end point and the safety end point of the trial.

METHODS

The study was conducted in accordance with the Declaration of Helsinki and its amendments or with the laws and regulations of the country in which the research was conducted, whichever afforded greater protection. Patients gave written informed consent for participation in the trial.

ELIGIBILITY CRITERIA

Patients 18 to 75 years of age were required to be fully recovered after surgery for histologically confirmed stage III colon carcinoma. Surgery had to have been performed within eight weeks before randomization. An Eastern Cooperative Oncology Group performance score of 0 or 1 (with a score of 0 indicating normal activity and 1 indicating the presence of symptoms but nearly full ambulatory capacity) and at least five years' life expectancy were required.

Patients with evidence of metastatic disease, including tumor cells in ascites or microscopic evidence of residual disease, were ineligible for participation. Macroscopic disease was ruled out with the use of abdominal pelvic computed tomography (CT) or magnetic resonance imaging (MRI) and chest radiography. Patients were also excluded on the basis of prior cytotoxic chemotherapy or organ allograft, clinically significant cardiac disease, severe renal impairment, central nervous system disorders, or pregnancy or lactation. Sexually active premenopausal women unwilling to practice contraception were ineligible.

STUDY DESIGN AND TREATMENT

The primary aim of the study was to show at least equivalence in disease-free survival between capecitabine and bolus fluorouracil plus leucovorin. Secondary end points included relapse-free survival, overall survival, and safety. Assessment of the rate of disease-free survival at three years was a prespecified secondary end point. Results with regard to the

quality of life are summarized here. The Quality of Life Questionnaire (QLQ-C30, version 2.0) of the European Organization for the Research and Treatment of Cancer was administered at baseline and before the start of the treatment cycles in weeks 7, 16, and 25 in the capecitabine group and weeks 9, 17, and 25 in the fluorouracil-plus-leucovorin group.

Patients were assigned to 24 weeks of treatment with either eight cycles of oral capecitabine, at a dose of 1250 mg per square meter of body-surface area, twice daily on days 1 through 14 every 21 days, or six cycles of rapid intravenous infusion of leucovorin, at a dose of 20 mg per square meter, followed immediately by an intravenous bolus of fluorouracil, at a dose of 425 mg per square meter, on days 1 through 5 every 28 days. Randomization, with the use of treatment allocation codes (scratch-off labels), was stratified by center and performed with a block size of four. The block size was unknown to investigators and monitors.

EVALUATION OF EFFICACY

Patients were assessed every six months for two years after randomization and then yearly. Each assessment was to include abdominal and pelvic CT or MRI and either thoracic radiography or thoracic CT or MRI. Disease-free survival was defined as the time between randomization and the first relapse, a second primary colon cancer, death from any cause when no evidence of relapse was recorded, or the last date at which the patient was known to be free of disease (censoring time). Relapse-free survival was defined as the time between randomization and the first relapse, a second primary colon cancer, death due to treatment-related toxic effects, or colon cancer if relapse had not been reported. Data on patients without documented relapse or with death unrelated to colon cancer or the study treatment were censored as of the last date on which the patient was known to be free of disease. Overall survival was defined as the time from randomization to death or the date at which the patient was last confirmed to be alive (censoring time).

EVALUATION OF SAFETY

The predefined primary end point for safety was at least equivalence as demonstrated through comparison of Kaplan–Meier estimates of the incidence and onset of all predefined severe (grade 3 or 4) toxic effects of the fluoropyrimidine (i.e., diarrhea, stomatitis, nausea, vomiting, hand–foot syndrome, alopecia, and neutropenia) in the two groups. Adverse

events were recorded as previously described.²⁶ The intensity of and adjustments to the dose of the study drug were recorded throughout treatment.

STATISTICAL ANALYSIS

The intention-to-treat population included all patients who underwent randomization. In accordance with the study protocol, the per-protocol population excluded patients receiving less than 12 weeks of treatment or less than 50 percent of the planned dose of the study drug during this initial period as well as those with major violations of inclusion or exclusion criteria. The population included in the safety analysis comprised all patients receiving at least one dose of the study drug who were followed up for safety. Results of the per-protocol analysis supported the same conclusions as the intention-to-treat analyses and are not presented.

The primary efficacy analysis was planned when 632 events for the end point of three-year disease-free survival had occurred in the per-protocol population. The use of a noninferiority margin of 1.25 for the hazard ratio and a type I error of 2.5 percent ensured 80 percent power to show at least equivalence between the two study treatments. Assuming three-year disease-free survival rates of 70 percent, and allowing for approximately 15 percent of patients to be excluded from the per-protocol population, an enrollment of 1956 patients was planned. A second hierarchical test evaluated equivalence in disease-free survival with an upper limit of the hazard ratio of 1.20. If these analyses proved to be positive, tests for superiority were planned. Analyses for at least equivalence were performed in the per-protocol and intention-to-treat populations; superiority analyses were performed only in the intention-to-treat population, to maintain the most conservative approach. No interim analyses were performed.

Disease-free survival and overall survival were analyzed with the use of proportional-hazards regression and presented as Kaplan–Meier estimates and hazard ratios with 95 percent confidence intervals. Relapse-free survival was analyzed with the use of proportional-hazards regression and presented as a cumulative-incidence plot and hazard ratios with 95 percent confidence intervals. Planned multivariate analyses to evaluate the robustness of the data on disease-free, relapse-free, and overall survival were based on proportional-hazards regression. Subgroup analyses of disease-free survival were also prospectively planned.

The study (trial M66001) was designed and initiated by investigators and employees of the sponsor, Hoffmann–La Roche. The data were collected, managed, and analyzed by the sponsor. The article was prepared by the primary author, with editorial assistance from a medical writer (who was not an employee of the sponsor), on the basis of data and statistical analyses provided by the sponsor. The contents were reviewed and approved by all authors. The decision to publish this report was made by the investigators and the sponsor. The sponsor placed no contractual restrictions on the publication of the data but retained the right to review them before submission of the manuscript for publication. Dr. Twelves vouches for the accuracy and completeness of this report.

RESULTS

PATIENT POPULATION AND FOLLOW-UP

Between November 1998 and November 2001, 1987 patients were enrolled at 164 centers worldwide. Of 1004 patients assigned to capecitabine, 12 percent were excluded from the per-protocol population, and of 983 patients assigned to fluorouracil plus leucovorin, 11 percent were excluded. The reasons for exclusion were balanced between the two groups. In both groups, the median follow-up was 3.8 years, which was the time from randomization to closing of the database for analysis (April 1, 2004). Overall, 33 patients were lost to follow-up (18 in the fluorouracil-plus-leucovorin group and 15 in the capecitabine group).

Baseline characteristics were similar in the two groups (Table 1). There were slightly more patients with carcinoembryonic antigen levels above the upper limit of normal at baseline in the capecitabine group than in the fluorouracil-plus-leucovorin group (8.6 percent vs. 7.0 percent). The proportion of patients with involvement of four or more regional lymph nodes (stage N2 disease), as opposed to involvement of one to three nodes (stage N1 disease), was slightly higher in the capecitabine group than in the fluorouracil-plus-leucovorin group (30.8 percent vs. 29.4 percent).

DISEASE-FREE SURVIVAL

Table 2 summarizes the results for the three major efficacy end points. The primary objective — the determination of whether capecitabine results in disease-free survival at least equivalent to that with fluorouracil plus leucovorin — was met (Fig. 1A). The

hazard ratio comparing disease-free survival in the capecitabine group with that in the fluorouracil-plus-leucovorin group was 0.87 (95 percent confidence interval, 0.75 to 1.00). The upper limit of the confidence interval (1.0) was significantly below both predefined margins, 1.25 and 1.20, for at least equivalence ($P < 0.001$ for both comparisons), providing confidence that capecitabine is at least as effective as fluorouracil plus leucovorin. The protocol-specified analysis for superiority showed a trend toward superior disease-free survival with capecitabine as compared with fluorouracil plus leucovo-

Table 1. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Capecitabine (N=1004)	Fluorouracil plus Leucovorin (N=983)
Sex (%)		
Male	54	54
Female	46	46
Age (yr)		
Median	62	63
Range	25–80	22–82
Age group (%)		
<70 yr	81	79
≥70 yr	19	21
ECOG performance score (%)		
0	85	85
1	15	15
Nodal status — (%)		
N1	69	71
N2	31	29
Tumor stage (%)†		
T1 or 2	10	10
T3	76	76
T4	14	14
Carcinoembryonic antigen level (%)		
≤ULN	83	85
>ULN	9	7
Missing data	8	8

* ECOG denotes Eastern Cooperative Oncology Group, and ULN upper limit of normal.

† Higher numbers indicate greater depth of tumor penetration through the bowel wall.

Table 2. Efficacy for the Major End Points over a Median Follow-up Period of 3.8 Years.*

End Point	Total No. of Patients	No. of Patients with Event	Hazard Ratio (95% CI)	P Value for Equivalence	P Value for Superiority
Disease-free survival					
Capecitabine	1004	348	0.87 (0.75–1.00)	<0.001†	0.05
Fluorouracil plus leucovorin	983	380			
Relapse-free survival					
Capecitabine	1004	327	0.86 (0.74–0.99)	—	0.04
Fluorouracil plus leucovorin	983	362			
Overall survival					
Capecitabine	1004	200	0.84 (0.69–1.01)	<0.001‡	0.07
Fluorouracil plus leucovorin	983	227			

* P values for equivalence are one-sided; P values for superiority were calculated with the use of the Wald chi-square test. CI denotes confidence interval.

† The upper limit of the hazard ratio was compared with the noninferiority margin of 1.20, as prespecified in the study protocol.

‡ The upper limit of the hazard ratio was compared with the noninferiority margin of 1.25, as prespecified in the study protocol.

rin ($P=0.05$). The difference between the three-year rates of disease-free survival (a prespecified end point) in the capecitabine group (64.2 percent) and in the fluorouracil-plus-leucovorin group (60.6 percent) was not significant ($P=0.12$).

RELAPSE-FREE SURVIVAL

The definition of relapse-free survival was similar to that of disease-free survival, except that patients without a documented relapse and patients who died from a cause unrelated to colon cancer or the study treatment were censored (21 events in the capecitabine group and 18 in the fluorouracil-plus-leucovorin group). Relapse-free survival in the capecitabine group was longer than in the fluorouracil-plus-leucovorin group ($P=0.04$; hazard ratio, 0.86; 95 percent confidence interval, 0.74 to 0.99). Figure 1B shows the cumulative incidence of relapse (or of death due to the study treatment or colon cancer in patients who had no evidence of relapse). The three-year rates of relapse-free survival (not a prespecified end point) were 65.5 percent in the capecitabine group and 61.9 percent in the fluorouracil-plus-leucovorin group ($P=0.12$).

OVERALL SURVIVAL

Overall survival in the two groups did not differ significantly ($P=0.07$) (Fig. 1C). The hazard ratio for death in the capecitabine group as compared with the fluorouracil-plus-leucovorin group was not statistically significant (0.84; 95 percent confidence in-

terval, 0.69 to 1.01). The three-year rates of overall survival (not a prespecified end point) were 81.3 percent and 77.6 percent in the capecitabine group and the fluorouracil-plus-leucovorin group, respectively ($P=0.05$).

MULTIVARIATE ANALYSES

Included in the prospectively planned multivariate analyses were potentially relevant factors (i.e., treatment, age, sex, nodal status, time from surgery to randomization, elevated carcinoembryonic antigen level) identified from previous trials.^{5,6,11} These analyses showed that treatment with capecitabine had a statistically significant effect on disease-free survival (hazard ratio, 0.826; 95 percent confidence interval, 0.709 to 0.962; $P=0.01$) and overall survival (hazard ratio, 0.788; 95 percent confidence interval, 0.643 to 0.964; $P=0.02$), as compared with treatment with fluorouracil plus leucovorin. Exploratory analyses suggested that the difference between the results of the multivariate analyses and the unadjusted efficacy analysis was driven by small imbalances in baseline levels of carcinoembryonic antigen and extent of nodal involvement, which favored the fluorouracil-plus-leucovorin group. Other significant variables associated with improved disease-free survival in the multivariate analyses included female sex (hazard ratio, 0.764; 95 percent confidence interval, 0.653 to 0.893), stage N1 disease (hazard ratio, 0.583; 95 percent confidence interval, 0.497 to 0.683), and normal carcinoembryonic antigen levels

(hazard ratio, 0.389; 95 percent confidence interval, 0.312 to 0.485).

SUBGROUP ANALYSES

Subgroup analyses of disease-free survival showed a consistent trend toward benefit from capecitabine over fluorouracil plus leucovorin among the subgroups categorized according to prognostic factors that were used in the multivariate analysis (Fig. 2).

TREATMENT

The median number of chemotherapy cycles received (during the planned 24-week course) was eight in the capecitabine group and six in the fluorouracil-plus-leucovorin group. Eighty-three percent of patients in the capecitabine group and 87 percent in the fluorouracil-plus-leucovorin group completed treatment as planned. The median dose intensity delivered was 93 percent of that planned for capecitabine and 92 percent of that planned for fluorouracil plus leucovorin. In 57 percent of patients receiving capecitabine and 52 percent of those receiving fluorouracil plus leucovorin, the dose of the study drug required modification (for delay, dose reduction, or interruption of treatment). In a similar proportion of patients receiving capecitabine or fluorouracil plus leucovorin, the dose required reduction (42 percent and 44 percent, respectively). More interruptions (15 percent vs. 5 percent) and delays (46 percent vs. 29 percent) were required with capecitabine. Nevertheless, most patients in the capecitabine group completed at least four of the eight chemotherapy cycles without a reduction in the dose of the medication (76 percent vs. 68 percent in the fluorouracil-plus-leucovorin group after three of the six chemotherapy cycles), supporting the use of the standard starting dose in this trial.

PRIMARY SAFETY END POINT

Safety data (excluding the primary safety end point) were reported comprehensively 19 months after the last patient was enrolled.²⁶ The onset of the predefined key grade 3 or 4 toxic effects was significantly reduced throughout treatment with capecitabine as compared with treatment with fluorouracil plus leucovorin ($P < 0.001$) (Fig. 3). The onset of toxic effects was also delayed with capecitabine as compared with fluorouracil plus leucovorin. Table 3 shows the incidence of the most common treatment-related clinical adverse events and laboratory abnormalities.

A score for global health status on the Quality of Life Questionnaire was prespecified as the primary

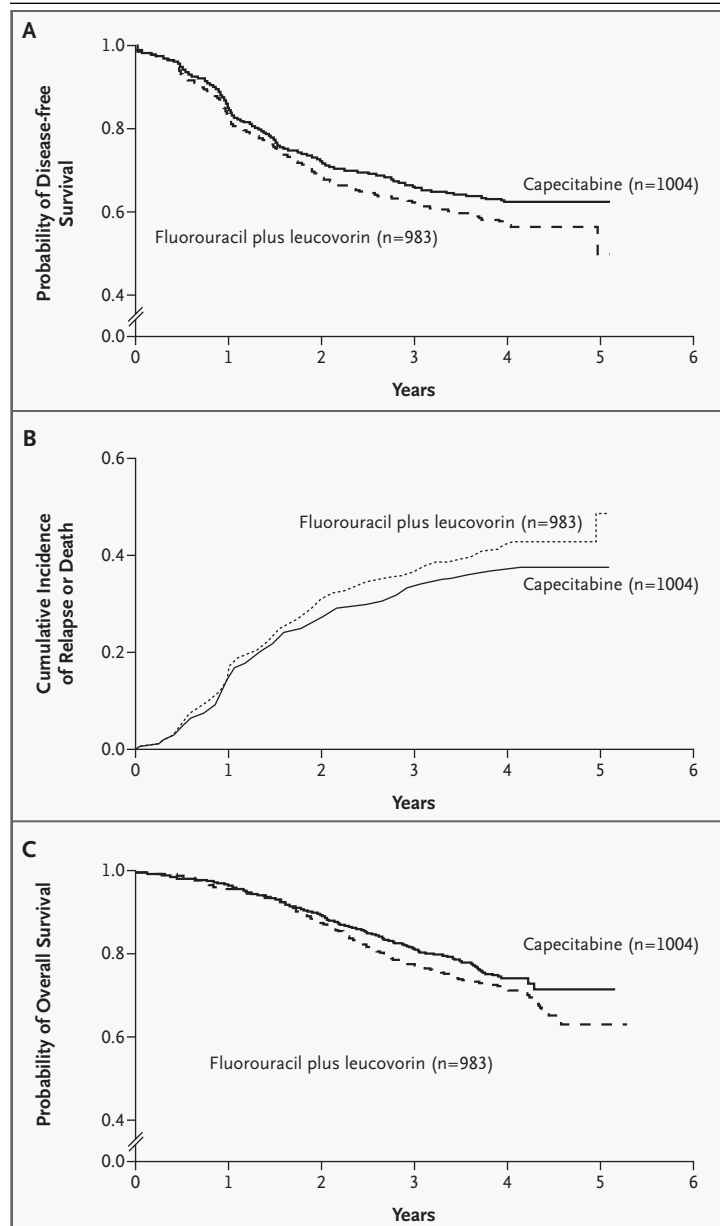


Figure 1. Disease-free Survival, Incidence of Relapse or Death, and Overall Survival among Patients Receiving Fluorouracil plus Leucovorin or Capecitabine (Intention-to-Treat Population).

Panel A shows Kaplan–Meier estimates of disease-free survival. The upper limit of the confidence interval of the hazard ratio was significantly below both the predefined margins, 1.25 and 1.20, for equivalence ($P < 0.001$ in both cases). The analysis for superiority showed a trend favoring capecitabine (hazard ratio, 0.87 [95 percent confidence interval, 0.75 to 1.00]; $P = 0.05$). Panel B shows the cumulative incidence of relapse or death; only deaths related to colon cancer or the study treatment were included. A Cox proportional-hazards model showed that relapse-free survival in the capecitabine group was statistically superior to that in the fluorouracil-plus-leucovorin group ($P = 0.04$; hazard ratio, 0.86; 95 percent confidence interval, 0.74 to 0.99). Panel C shows Kaplan–Meier estimates of overall survival. The analysis for survival showed a trend favoring capecitabine (hazard ratio, 0.84 [95 percent confidence interval, 0.69 to 1.01]; $P = 0.07$).

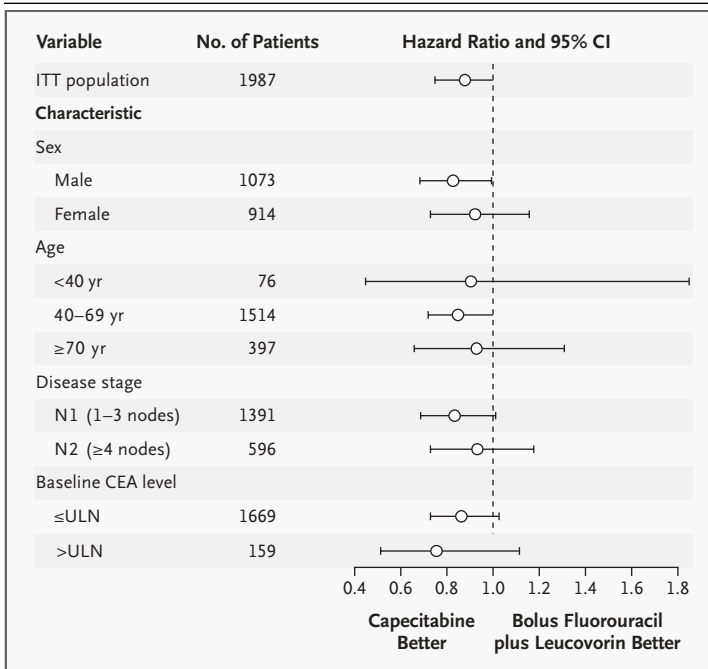


Figure 2. Subgroup Analysis of Disease-free Survival in the Capecitabine Group as Compared with the Fluorouracil-plus-Leucovorin Group (Intention-to-Treat Population).

Data on carcinoembryonic antigen (CEA) levels were missing for 159 patients who were therefore not included in the analysis for this variable. ITT denotes intention to treat, N nodal status, and ULN upper limit of normal.

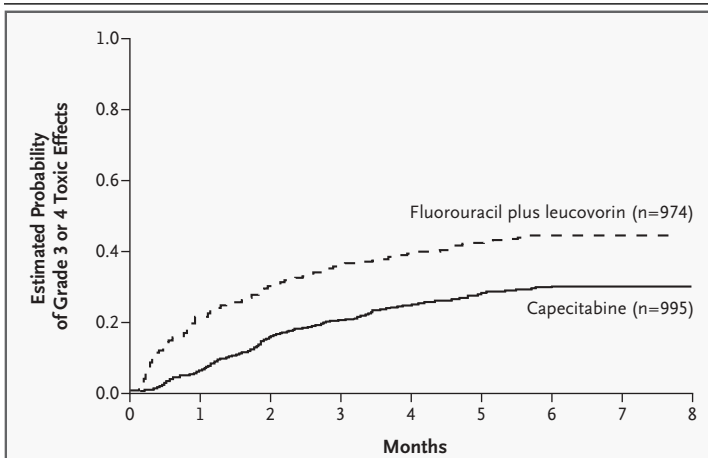


Figure 3. Kaplan-Meier Estimates of the Onset of Predefined Key Grade 3 or 4 Toxic Effects of Fluoropyrimidine.

P<0.001 for the difference between the groups.

measure of the quality of life. In the two groups, the scores remained relatively constant over time. However, at week 25 of treatment, the mean scores for global health status in the two groups showed similar small increases from baseline (<5 percent in raw scores), indicating improvement in the quality of life.

DISCUSSION

This randomized phase 3 trial showed that disease-free survival among patients who received oral capecitabine was at least equivalent to that among those who received fluorouracil plus leucovorin by intravenous bolus as adjuvant treatment for stage III colon cancer. Predefined multivariate analyses reinforced the primary efficacy findings. Although unadjusted analyses of disease-free survival and overall survival showed noninferiority of capecitabine to fluorouracil plus leucovorin, the multivariate analyses suggested that treatment with capecitabine improved the efficacy outcomes. We speculate that small imbalances in the two baseline characteristics with the strongest prognostic influence (i.e., elevated carcinoembryonic antigen levels and nodal status), which favored the fluorouracil-plus-leucovorin group, may have reduced the effect of capecitabine in the unadjusted analyses. Multivariate analyses also confirmed the prognostic significance of female sex, extent of nodal involvement, and elevated baseline carcinoembryonic antigen levels with regard to the three efficacy end points identified in previous trials; as expected, age influenced only overall survival. The only factor identified from previous trials that did not influence outcomes in the current study was time from surgery to randomization. However, because the eligibility criteria in this trial specified an interval of eight weeks or less between surgery and randomization, variability in this measure was limited in ours as compared with earlier trials.

The results with the Mayo Clinic regimen in our trial were consistent with those in previous studies. If patients with disease stage III are isolated from the more mixed population of the INT-0089 trial,⁸ which is the only other study of similar size using this regimen, the three-year disease-free survival rate (63 percent) is similar to that in the group receiving the Mayo Clinic regimen in the current trial.

The significantly lower incidence and delayed

onset of fluoropyrimidine-related grade 3 or 4 toxic effects with capecitabine as compared with fluorouracil plus leucovorin supports the favorable safety data reported with regard to patients with metastatic disease.²⁶ Overall, there were significantly lower incidences of neutropenia and stomatitis and lower rates of nausea, vomiting, alopecia, and diarrhea in the settings of adjuvant treatment and metastatic disease with capecitabine.²⁶ The incidence of grade 3 hand-foot syndrome was, however, significantly higher with capecitabine than with fluorouracil plus leucovorin. The higher number of dose delays and interruptions of treatment in the capecitabine group reflected the schedule of twice-daily oral administration. An important element in this approach is educating patients to recognize toxic effects of grade 2 or greater severity and interrupting treatment promptly.

The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (better known as MOSAIC) trial showed that adding oxaliplatin to infused fluorouracil plus leucovorin provides a 23 percent reduction in the risk of recurrence, which is a significant and clinically meaningful benefit.²⁷ Analysis of the survival data is premature, but a meta-analysis of the use of adjuvant fluorouracil has shown that disease-free survival is predictive of overall survival.²⁸ The safety of infused fluorouracil, leucovorin, and oxaliplatin was acceptable, but peripheral neuropathy, myelosuppression, and gastrointestinal disturbances were significantly more common among those also receiving oxaliplatin than among those receiving infused fluorouracil plus leucovorin alone.

The X-ACT trial shows that capecitabine is at least equivalent to the Mayo Clinic regimen of fluorouracil plus leucovorin in patients younger than 70 years and those 70 years of age or older. The safety advantage of capecitabine over fluorouracil plus leucovorin was also maintained in these subgroups.²⁹ Our results support capecitabine as an alternative to fluorouracil plus leucovorin in the adjuvant treatment of colon cancer. Capecitabine or

Table 3. Most Common Treatment-Related Adverse Events.*

Event	All Grades of Events		Grade 3 or 4 Events (Severe)	
	Capecitabine (N=995)	Fluorouracil plus Leucovorin (N=974)	Capecitabine (N=995)	Fluorouracil plus Leucovorin (N=974)
	<i>percent</i>			
Diarrhea	46†	64	11	13
Nausea or vomiting	36†	51	3	3
Stomatitis	22†	60	2†	14
Hand-foot syndrome	60†	9	17†	<1
Fatigue or asthenia	23	23	1	2
Abdominal pain	10	13	2	1
Alopecia	6†	22	0‡	<1
Lethargy	10	9	<1	<1
Anorexia	9	10	<1	<1
Neutropenia§	32†	63	2†	26
Hyperbilirubinemia§	50†	20	20†	6

* Treatment-related adverse events that occurred in 10 percent or more of patients were included in the safety analysis. The data shown are an update to the data of Scheithauer et al.²⁶

† P<0.001.

‡ P=0.02.

§ Diagnosis was based on laboratory values.

oxaliplatin-based therapy should be considered for all patients requiring adjuvant therapy for colon cancer.

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APPENDIX

The following investigators participated in the X-ACT trial. **Argentina** — E. Mickiewicz, G. Pallotta, E. Roca, M.S. Varela, R.C. Wainstein; **Australia** — E. Abdi, A. Barling, S. Begbie, D. Bell, R. Blum, W.I. Burns, P. de Souza, D. Kotasek, J. Levi, K. Pittman, M. Schwarz, C. Underhill, D. Wyld; **Austria** — P. Balcke, M. Baur, D. Geissler, P. Kier, H. Ludwig, K. Mach, D. Öfner, M. Prager, H. Steiner; **Belgium** — J. De Grève, D. Vanstraelen; **Brazil** — L. Camillo-Coura, G. Delgado, S. Lago, A. Malzyner, C. Rotstein; **Canada** — J.P. Ayoub, O. Keller, K. Khoo, R. Rajan, A. Sami, R. Wong; **Croatia** — M. Duvnjak, Z.K. Osijek, R. Ostojic, E. Vrdoljak; **Czech Republic** — I. Bustova, J. Dvorak, J. Fínek, I. Kocakova, M. Kúta, J. Nemeč, V. Svoboda, P. Vodvarka; **France** — F.X. Caroli-Bosc, G. Dabouis, J.-Y. Douillard, P. Dufour, E. Gamelin, J.L. Gaudin, M. Giovannini, H. Gouerou, J.E. Kurtz, C. Lombard-Bohas, D. Peré-Vergé, M. Ychou; **Germany** — W. Abenhardt, A. Beham, R. Behrens,

W. Brugger, R. Heinze, W.D. Hirschmann, K.W. Jauch, E. Kettner, M. Mayr, B. Otremba, H. Riess, J. Rüschoff, M. Schmidt, H. Tesch, B. Tschenechne, M. Wolf; **Greece** — L. Boutis, G. Fountzilas, I. Katsos, G. Panagos; **Israel** — D. Aderka, A. Benni, A. Figer, B. Klein, A. Shani, S. Stemmer; **Italy** — M. Airolidi, G. Amadori, M. Antimi, C. Barone, O. Bertetto, M. Bertuccelli, G. Biasco, C. Bumma, G. Comella, P. Conte, F. Di Costanzo, C.M. Foggi, V. Fossier, S. Frustaci, G. Gasparini, R. Labianca, G. Luppi, M. Marco, D. Mecarocci, A. Paccagnella, C. Rabbi, S. Ricci, A. Scanni, V. Silingardi, F. Smerieri, O. Vinante; **Latvia** — A. Brīze, G. Purkalne; **Poland** — M. Foszyczynska-Kloda, H. Karnicka-Mlodkowska, K. Lesniewski-Kmak; **Portugal** — P. Cortes, B. da Costa, J. Maurício, E. Sanches; **Serbia** — S. Jelic; **Spain** — E. Aranda, R. Cubedo, E. Díaz-Rubio, A. Lozano, H. Manzano, P. Martinez del Prado, R. Pérez Carrión, G. Pérez-Manga, J.J. Valerdi, J.J. Valverde, A. Velasco; **Sweden** — G. Borghede, H. Grönberg, B. Gustavson, T. Linné, B. Löden, B. Norberg, H. Starkhammar, J.-H. Svensson; **Switzerland** — M. Borner, R. Hermann, D. Köberle, R. Morant, O. Pagani, C. Sessa, R. Stahel; **Thailand** — S. Chakrapee-Sirisuk; **United Kingdom** — N. Bailey, F. Coxon, F. Daniel, D. Dunlop, T. Iveson, R. James, P. Johnston, E. Levine, A. Makris, T. Maughan, A. McDonald, L. Samuel, M. Soukop, W. Stewart, C. Topham, M. Verrill; **Uruguay** — I.M. Muse; **United States** — J. Eckardt, G. Gross, G. Justice, L. Kalman, R. Kerr, C.G. Leichman, E. Levine, V. Malhotra, R. Pelley, M.C. Perry, J. Posey, M. Saleh, J. Salvatore, J. Wooldridge.

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