Xeloda® in Adjuvant Colon Cancer Therapy (X-ACT) Trial: Overview of Efficacy, Safety, and Cost-Effectiveness

Chris J. Twelves on behalf of the X-ACT Investigators

Abstract

The X-ACT (Xeloda® in Adjuvant Colon Cancer Therapy) trial compared the efficacy and safety of the oral fluoropyrimidine capecitabine with bolus 5-fluorouracil (5-FU)/leucovorin (LV; Mayo Clinic regimen) as adjuvant therapy for stage III colon cancer. A total of 1987 patients were enrolled at 164 centers worldwide. Disease-free survival (primary study endpoint) in the capecitabine arm was at least equivalent to that in the 5-FU/LV arm; the upper limit of the hazard ratio was significantly ($P < 0.001$) below the predefined margins for noninferiority. Capecitabine was also associated with significantly fewer fluoropyrimidine-related grade 3/4 adverse events (AEs; $P < 0.001$) and fewer AE-related hospital admissions/days than 5-FU/LV. Pharmacoeconomic analyses performed in several countries show that the savings in direct costs (drug administration and AE-related costs) associated with capecitabine versus 5-FU/LV offset the acquisition costs of the drug. Furthermore, capecitabine reduces patient travel time and costs, making it a "dominant" strategy (ie, less costly and more effective) in the adjuvant setting. In conclusion, efficacy, safety, convenience, and cost findings from the X-ACT trial show that capecitabine offers at least equivalent clinical benefit compared with bolus 5-FU/LV and can replace intravenous 5-FU/LV in the adjuvant treatment of stage III colon cancer. The X-ACT trial has not only helped to better define the role of capecitabine but has also broadened the options available to patients with early-stage disease to include a uniquely effective oral outpatient treatment.

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Introduction

Fluoropyrimidines are an integral part of the adjuvant treatment of colon cancer. The standard of care for adjuvant therapy in colon cancer has been 5-fluorouracil (5-FU)/leucovorin (LV) administered for 6-8 months based on findings from landmark trials showing 22%[1] and 33%[2] reductions in mortality with 5-FU/LV versus surgery alone.

Although there is consensus regarding the use of 5-FU/LV, there is no accepted standard schedule. Survival benefits with intravenous (I.V.) bolus regimens of 5-FU/LV are evident whether treatment is given daily for 5 days per month (Mayo Clinic regimen) or as a weekly schedule (Roswell Park regimen).[2-5] Subsequent studies investigating infusional regimens failed to identify any improvements in efficacy versus bolus 5-FU/LV, although improvements in tolerability were evident.[6-8] Consequently, the Mayo Clinic regimen is the most widely used 5-FU/LV administration schedule and is advocated by licensing authorities to be used as a reference regimen for trials of adjuvant therapy.

Capecitabine is an oral fluoropyrimidine that generates 5-FU preferentially in tumor tissue through a 3-step enzymatic cascade.[9] It is administered twice daily to produce plasma levels resembling more closely those of a protracted infusion of 5-FU than a bolus schedule. As first-line therapy for metastatic colorectal cancer (CRC), oral capecitabine achieved improved response rates (26% vs. 17%, respectively) and equivalent disease-free survival (DFS) and overall survival (OS) compared with 5-FU/LV (Mayo Clinic regimen).[10] These data, together with the improved tolerability profile offered by capecitabine compared with 5-FU/LV[11] and the convenience of oral administration, have meant that

University of Leeds and Bradford National Health Service Foundation Trust, United Kingdom

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Address for correspondence: Chris J. Twelves, MD, Institute for Cancer Therapeutics, University of Bradford, BD7 1DP, United Kingdom
Fax: 44-1274-235896; e-mail: c.twelves@bradford.ac.uk

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Table 1 X-ACT Trial Methodology[11,14,15]

Study Design	International, multicenter, randomized, open-label, parallel-group phase III trial.
Study Objectives	To show that capecitabine achieves at least equivalent DFS to 5-FU/LV (Mayo Clinic regimen).
	Secondary outcomes were OS, quality of life, medical resource utilization, and safety profile.
Selection Criteria	Patients aged 18-75 years who were fully recovered from surgery for stage III colon carcinoma; surgery had to have been performed within 8 weeks before randomization.
Adjuvant Therapy	Patients received 24 weeks of treatment with oral capecitabine 1250 mg/m^2 twice daily, given on days 1-14 every 21 days, or I.V. LV 20 mg/m^2 by rapid infusion followed immediately by I.V. bolus 5-FU 425 mg/m^2, days 1-5 every 28 days. Dose modification schemes were as described by Cassidy et al.[11] The protocol was amended after the inclusion of 1363 patients to reduce the capecitabine starting dose by 25% in patients with moderate renal impairment (creatinine clearance, 30-50 mL per minute) based on data published at that time.[11,14]
Efficacy Evaluation	Performed every 6 months for 2 years and annually thereafter. Each assessment included abdominal and pelvic computed tomography, magnetic resonance imaging and thoracic radiography, or thoracic computed tomography or magnetic resonance imaging.
Safety Evaluation	Safety data were collected during treatment and for 28 days after the last intake of study drug. Adverse events were graded according to National Cancer Institute of Canada Common Toxicity Criteria. Hand-foot syndrome was graded as described by Van Cutsem et al.[15] Laboratory analyses were performed at the beginning of each cycle.
Resource Use	Medical resource utilization data were collected during treatment and for 28 days after the last intake of study drug. Data included study drug administration (cumulative dose, infusion duration, and frequency), hospital admissions (including length of stay), and visits to providers and outpatient consultations for treatment-related AEs.
Endpoint Definitions	DFS: 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).
	RFS: time between randomization and the first relapse, a second primary colon cancer, death from 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.
	OS: time from randomization to death or the date at which the patient was last confirmed to be alive (censoring time).

capecitabine is now replacing 5-FU/LV as the backbone of therapy in many gastrointestinal cancers.

The X-ACT (Xeloda® in Adjuvant Colon Cancer Therapy) trial was undertaken to compare the efficacy and tolerability of oral capecitabine with bolus I.V. 5-FU/LV (Mayo Clinic regimen) as adjuvant therapy for patients with stage III (Dukes C) colon cancer.[12,13] This review presents the full efficacy and safety results from this trial, together with details of subsequent pharmacoeconomic analyses performed using medical resource utilization and survival data from the X-ACT trial. As a result of the X-ACT trial data, capecitabine has received approval from the European Medicines Agency Committee for Medicinal Products for Human Use and the US Food and Drug Administration for the adjuvant treatment of colon cancer.

Key Findings from the X-ACT Trial

The X-ACT trial was designed to demonstrate that capecitabine achieves at least equivalent DFS to I.V. bolus 5-FU/LV (Mayo Clinic regimen) when administered as adjuvant therapy after surgery for stage III or Dukes stage C colon cancer. The methodologic details of the trial are summarized in Table 1.[11,14,15]

From November 1998 to November 2001, a total of 1987 patients were enrolled into the X-ACT trial at 164 centers worldwide. The capecitabine and 5-FU/LV treatment arms included 1004 and 983 patients, respectively, and were well matched (Table 2).[12] Of note, only 35 patients (< 2%) were recruited from North America.

Efficacy Outcomes

Disease-Free Survival: Strong Trend Toward Superiority with Capecitabine Versus 5-FU/LV

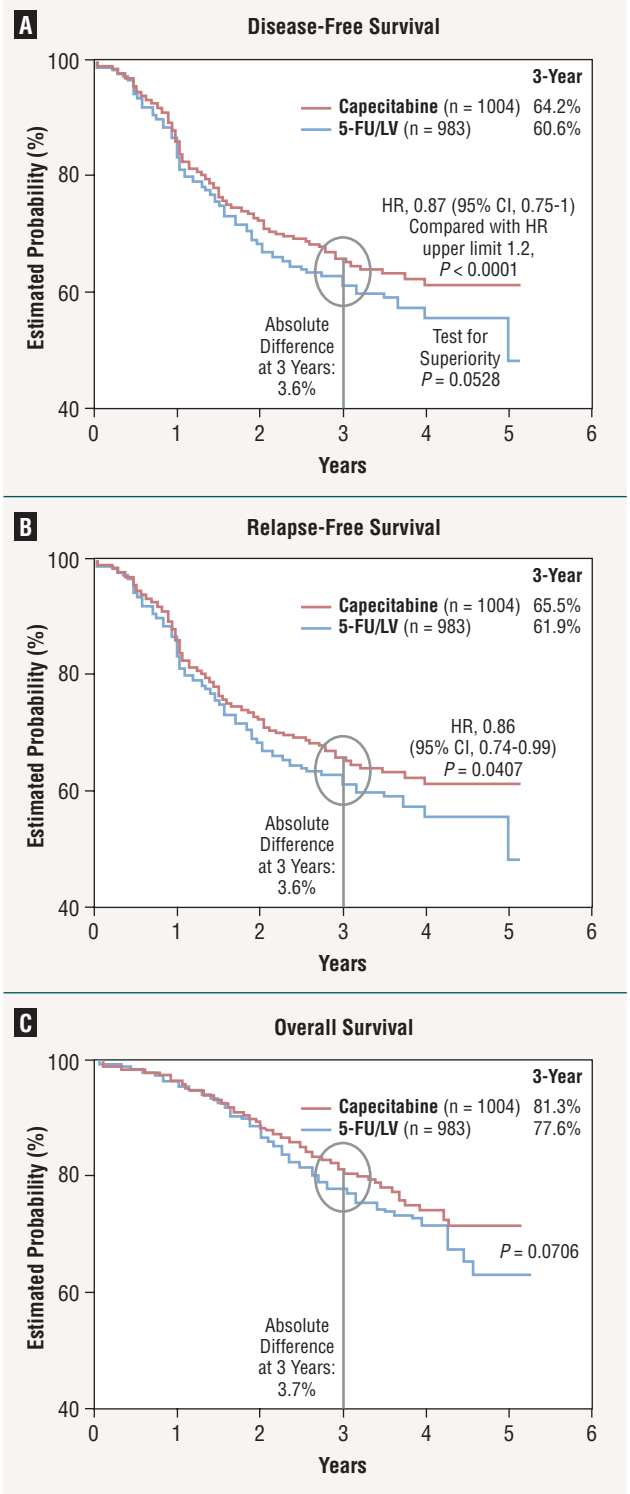
The X-ACT trial clearly met its primary objective, ie, to demonstrate at least equivalent DFS with capecitabine and 5-FU/LV, with a hazard ratio (HR) in the intent-to-treat (ITT) population of 0.87 (95% confidence interval [CI], 0.75-1; Figure 1A), favoring capecitabine. The upper limit of the CI was significantly ($P < 0.0001$) less than both of the predefined margins of 1.25 and 1.2 for, at least, equivalence. Therefore, these data provide a high level of confidence that capecitabine is at least equivalent to I.V. 5-FU/LV, with a P value excluding inferiority of $P < 0.0001$.

Because the primary objective of the study was met, a prospectively planned test for superiority was also performed. In this analysis, capecitabine showed a strong trend toward superior DFS compared with 5-FU/LV in the ITT population ($P = 0.0528$). The 3-year DFS rates were 64.2% with capecitabine and 60.6% with 5-FU/LV, giving an absolute difference of 3.6% (95% CI, –1 to 8.1; $P = 0.12$) between treatments.

Relapse-Free Survival: Superior with Capecitabine Versus 5-FU/LV

Relapse-free survival (RFS), a secondary endpoint of the trial, differs slightly from DFS in that it takes only colon cancer–specific events into consideration (see Table 1 for endpoint definitions). Relapse-free survival in the ITT population was statistically superior with capecitabine versus 5-FU/LV (HR, 0.86; 95% CI, 0.74-0.99; $P = 0.0407$; Figure 1B). The 3-year RFS rates were 65.5%

Figure 1 Kaplan-Meier Estimates of Disease-Free, Relapse-Free, and Overall Survival



Kaplan-Meier estimates of (**A**) DFS, (**B**) RFS, and (**C**) OS in patients with stage III colon cancer receiving 5-FU/LV and capecitabine as adjuvant therapy (intent-to-treat population). For DFS, the upper limit of the CI of the HR was significantly below the predefined margins, 1.25 and 1.2, for equivalence ($P < 0.001$ in both cases). The analysis for superiority showed a trend favoring capecitabine (HR, 0.87; 95% CI, 0.75-1; $P = 0.05$). For RFS, a Cox proportional hazards model showed that RFS in the capecitabine group was statistically superior to that in the 5-FU/LV group (HR, 0.86; 95% CI, 0.74-0.99; $P = 0.0407$). For OS, the analysis for survival showed a trend favoring capecitabine (HR, 0.84; 95% CI, 0.69-1.01; $P = 0.0706$).

Table 2 Baseline Characteristics of Patients in the X-ACT Trial (Intent-to-Treat Population)[12]

Characteristic	Capecitabine (n = 1004)	5-FU/LV (n = 983)
Sex		
Male	54	54
Female	46	46
Median Age, Years (Range)	62 (25-80)	63 (22-82)
< 70	81	79
≥ 70	19	21
ECOG PS Score		
0	85	85
1	15	15
CEA		
Normal	83	85
> 1 × upper limit of normal	9	7
Data missing	8	8
Tumor Stage		
T1/2	10	10
T3	76	76
T4	14	14
Nodal Status		
N1	69	71
N2	31	29
Tumor Differentiation		
Well	9	10
Moderate	65	63
Poor	16	19
Anaplastic	1	1

Values are percentages unless otherwise indicated.
Abbreviation: ECOG = Eastern Cooperative Oncology Group

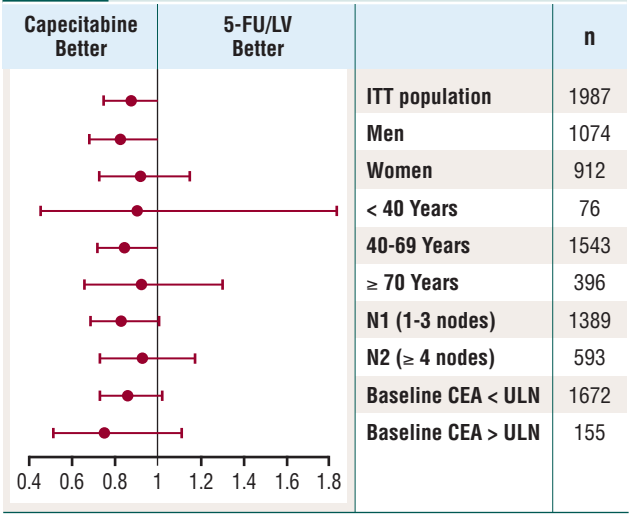
with capecitabine and 61.9% with 5-FU/LV, giving an absolute difference of 3.6% (95% CI, –0.9-8.1; $P = 0.12$).

Overall Survival: Trend Toward Improvement with Capecitabine Versus 5-FU/LV

There was a trend toward improved OS ($P = 0.0706$) in the ITT population with capecitabine versus 5-FU/LV (Figure 1C). The HR for capecitabine versus 5-FU/LV was 0.84 (95% CI, 0.69-1.01), which translates into a 16% reduction in the risk of death for patients receiving capecitabine. The 3-year OS rates were 81.3% with capecitabine and 77.6% with 5-FU/LV, giving an absolute difference of 3.7% (95% CI, –0.1 to 7.5; $P = 0.05$) between treatment groups.

Results of the per-protocol analyses (which excluded patients receiving < 12 weeks of treatment or < 50% of the planned doses of the study drug, as well as those with major violations of inclusion or exclusion criteria) supported the same conclusions as the ITT analyses.

Figure 2 Subgroup Analysis of DFS with Capecitabine Versus 5-FU/LV[12]



An analysis of post-study treatments received by patients, the data for which were collected prospectively, showed that both treatment groups were well matched with regard to first- and second-line therapy for metastatic disease, as well as radiation therapy and surgery (Table 3).[16] These data suggest that any post-study treatments were unlikely to have influenced OS in the X-ACT trial.

Multivariate and Subgroup Analyses: Confirm Robustness of Primary Efficacy Findings

Prospectively planned multivariate analyses using proportional-hazards regression were performed to assess the robustness of the primary efficacy findings. Potentially influential factors considered in the analysis, namely treatment, age, sex, nodal status, time from surgery to randomization, and carcinoembryonic antigen (CEA) levels, were identified from previous landmark trials.[1,2,6]

The multivariate analyses showed that treatment with capecitabine had a statistically significant effect on DFS (HR, 0.826; 95% CI, 0.709-0.962; P = 0.01) as well as OS (HR, 0.788; 95% CI, 0.643-0.964; P = 0.02) compared with 5-FU/LV. In fact, the multivariate analyses favored capecitabine more strongly for all 3 efficacy endpoints compared with the unadjusted efficacy analyses. Differences between the multivariate and unadjusted efficacy analyses might have been driven by small imbalances in baseline levels of CEA levels and nodal status (Table 2).[12] Specifically, there were slightly more patients with baseline CEA levels above the upper limit of normal in the capecitabine group versus the 5-FU/LV group (9% vs. 7%), and the proportion of patients without N1 disease was slightly higher in the capecitabine arm (31% vs. 29% with 5-FU/LV).[12]

Other variables significantly associated with improved DFS were female sex (HR, 0.764; 95% CI, 0.653-0.893), stage N1 disease (HR, 0.583; 95% CI, 0.497-0.683), and normal CEA levels (HR, 0.389; 95% CI, 0.312-0.485).

Table 3 Post-Study Cancer-Related Treatment[15]

Post-Study Treatment	% of Patients	
	Capecitabine (n = 1004)	5-FU/LV (n = 983)
Metastatic		
First-line	23	26
Irinotecan-based	42	34
Oxaliplatin-based	31	26
5-FU/LV–based	22	22
Capecitabine	4	9
Other	4	6
Second-line	9	11
Irinotecan-based	38	40
Oxaliplatin-based	39	33
5-FU/LV–based	10	7
Capecitabine	2	11
Other	13	9
≥ Third-line	4	3
Additional Adjuvant	3	1
Other*	1	2
Radiation Therapy	6	6
Surgery	18	18

*Chemotherapy for non-colon cancer.

A prospectively planned subgroup analysis showed that capecitabine provided a consistent trend toward improved DFS versus 5-FU/LV across all prognostic subgroups identified by multivariate analysis (Figure 2).[12]

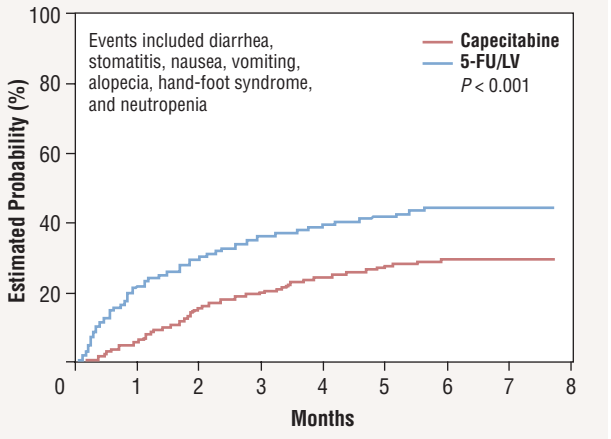
Safety Outcomes

Key Grade 3/4 Adverse Events: Later and Lower Rate with Capecitabine Versus 5-FU/LV

Consistent with the favorable safety data reported by Cassidy et al[10] in the metastatic setting, the tolerability profile of capecitabine was again found to be superior to that of I.V. bolus 5-FU/LV in the X-ACT trial.[12,13] The predefined primary safety endpoint of the study, ie, at least equivalence between treatments in the rate and onset of all predefined severe (grade 3/4) fluoropyrimidine-related adverse events (AEs; ie, diarrhea, stomatitis, nausea, vomiting, hand-foot syndrome, alopecia, and neutropenia) was exceeded. Kaplan-Meier analysis of the data showed that the overall probability of these predefined toxicities was significantly lower with capecitabine compared with 5-FU/LV (P < 0.001; Figure 3).[12]

These results are consistent with the most recent tolerability data from the X-ACT trial (Table 4)[12] and a prospectively planned safety analysis, which was conducted 19 months after enrollment of the last patient.[13] These data show that patients receiving capecitabine experienced significantly less diarrhea (46% vs. 64%), nausea/vomiting (36% vs. 51%), stomatitis (22% vs. 60%), and alopecia (6% vs. 22%) than those receiv-

Figure 3 Kaplan-Meier Estimates of the Onset of Predefined Key Fluoropyrimidine-Related Grade 3/4 Adverse Events[12]



P < 0.001 for the difference between treatment groups.

Table 4 Most Common (≥ 10% of Patients) Treatment-Related Adverse Events[12]

Event	% of Patients			
	All-Grade Events		Grade 3/4 Events	
	Capecitabine (n = 995)	5-FU/LV (n = 974)	Capecitabine (n = 995)	5-FU/LV (n = 974)
Diarrhea	46*	64	11	13
Nausea/Vomiting	36*	51	3	3
Stomatitis	22*	60	2*	14
Hand-Foot Syndrome	60*	9	17*	< 1
Fatigue/Asthenia	23	23	1	2
Alopecia	6*	22	0†	< 1
Abdominal Pain	10	13	2	1
Lethargy	10	9	< 1	< 1
Anorexia	9	10	< 1	< 1
Neutropenia	32*	63	2*	26
Hyperbilirubinemia‡	50*	20	20*	6

*P < 0.001.
†P = 0.02.
‡Grade 3: increased bilirubin concentrations ≤ 3 times the upper limit of normal; grade 4: increased bilirubin concentrations > 3 times the upper limit of normal.

ing 5-FU/LV (Table 4; *P* < 0.001 for all comparisons).[12] Febrile neutropenia/sepsis was also significantly less common in patients receiving capecitabine (0.3% vs. 3%; *P* < 0.001). The only treatment-related AE occurring more frequently with capecitabine was hand-foot syndrome (60% vs. 9% with 5-FU/LV for any-grade events; 17% vs. < 1% for grade 3 events; *P* < 0.001).

With regard to laboratory events, the overall rate of neutropenia (all grades) was significantly lower with capecitabine versus 5-FU/LV (32% vs. 63%; *P* < 0.001; Table 4).[12] Grade 3/4 neutropenia was also significantly less common with capecitabine compared with 5-FU/LV (2% vs. 26%; *P* < 0.001). Grade 3/4 hyperbilirubinemia was more common with capecitabine (20% vs. 6%; *P* < 0.001), although the clinical significance of this event is uncertain. However, the rate of grade 3/4 abnormalities in aspartate aminotransferase and alanine aminotransferase in both treatment arms was low (0.7% and 1.6%, respectively, with capecitabine; and 0.3% and 0.6%, respectively, with 5-FU/LV).

Premature withdrawal because of AEs occurred in 11% of patients receiving capecitabine and 7% of those receiving 5-FU/LV. This difference was largely because of more cases of withdrawal for hand-foot syndrome in capecitabine-treated patients (32 patients, 3%) compared with those receiving 5-FU/LV (4 patients, < 1%). There were 3 treatment-related deaths (0.3%) in the capecitabine arm (multi-organ failure, septic shock, and pneumonia, 1 patient each), and 4 deaths (0.4%) in the 5-FU/LV treatment arm (severe diarrhea and vomiting, respiratory arrest, gastrointestinal hemorrhage, and bronchopneumonia, 1 patient each). Overall, there was a low rate of all-cause, 60-day mortality, with 5 deaths in the capecitabine arm (0.5%) and 4 in the 5-FU/LV arm (0.4%).[13]

Cardiac Adverse Events: Similar in Both Groups

In the X-ACT trial, the rate of all-grade cardiac events (unrelated and related to treatment) was the same for capecitabine and 5-FU/LV (3% in both treatment arms), as were the rates of events pooled according to cardiac disease category (ischemic heart disease, arrhythmias, and congestive heart disease; Table 5). This finding is consistent with a retrospective analysis of phase III data from patients with metastatic CRC (n = 1189), which reported treatment-related cardiotoxic events in 3% of patients treated with capecitabine or bolus 5-FU/LV.[17]

The overall rates of grade 3/4 events, serious cardiac events, and events requiring treatment/intervention or hospitalization were also the same for capecitabine- and 5-FU/LV–treated patients (Table 5). In both treatment groups, a greater percentage of patients with a history of cardiac disease had ≥ 1 adverse cardiac event during treatment than patients with no history of cardiac disease (capecitabine-treated patients: 8 of 132 patients [6%] with a history of cardiac disease and 20 of 863 [2%] with no history; 5-FU/LV–treated patients: 15 of 117 [13%] and 18 of 857 patients [2%], respectively).

Dose Modifications: Similar in Both Groups

In the X-ACT trial, the median number of cycles of chemotherapy administered was 8 with capecitabine and 6 with 5-FU/LV. Eighty-three percent of patients on capecitabine and 87% on 5-FU/LV completed the full 24-week course of treatment. Median dose intensity was 93% of the planned dose for capecitabine and 92% for 5-FU/LV.

Overall, 57% of patients receiving capecitabine and 52% receiving 5-FU/LV required some sort of dose modification (delay, reduction, or interruption). Dose reduction was required in 42% of patients receiving capecitabine compared with 44% of patients receiving 5-FU/LV. However, the median time to first dose reduction was almost 2-fold longer

Table 5 Summary of Cardiac Disorder Events

Event	% of Patients	
	Capecitabine (n = 995)	5-FU/LV (n = 974)
All-Grade Events		
Total patients with ≥ 1 event	3	3
Ischemic heart disease	1	1
Arrhythmias	2	2
Congestive heart disease	< 1	< 1
Total number of events	29	34
Grade 3/4 Events		
Total patients with ≥ 1 event	1	1
Total number of events	12	11
Serious Events		
Total patients with ≥ 1 event	1	1
Total number of events	13	11
Events Requiring Treatment/ Intervention		
Total patients with ≥ 1 event	1	2
Total number of events	13	18
Events Requiring Hospitalization		
Total number of events	9	8

for patients receiving capecitabine compared with 5-FU/LV (78 days vs. 41 days). Second-level dose reductions (to < 60% of the capecitabine starting dose and < 75% of the 5-FU/LV starting dose) were less common with capecitabine than 5-FU/LV (13% vs. 26%); median time to second-level dose reduction was again longer for patients receiving capecitabine (113 days vs. 57 days with 5-FU/LV). The AEs most commonly leading to dose modification were hand-foot syndrome (31%) and diarrhea (15%) in capecitabine recipients and stomatitis (23%) and diarrhea (19%) in 5-FU/LV recipients.[13]

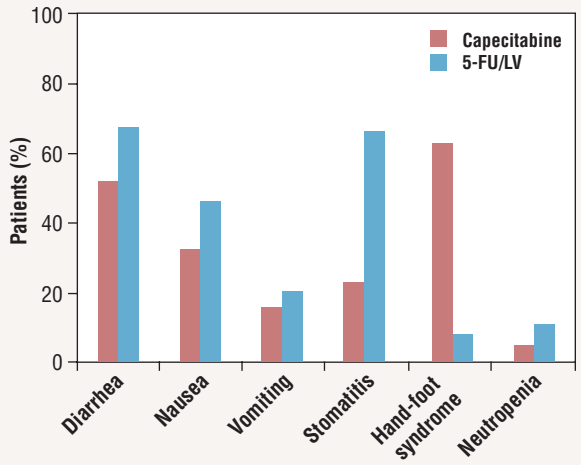
Efficacy and Safety Maintained in the Elderly

Clinical trials investigating the use of chemotherapy in patients with colon cancer are often criticized because the results are not stratified according to age and not enough elderly patients are included. In the X-ACT trial, 20% of the total patient population was aged ≥ 70 years, which permitted a comparative analysis of the efficacy and safety of capecitabine and 5-FU/LV in this age group.[18]

According to multivariate analysis, age did not influence DFS ($P = 0.901$; HR, 0.999) or RFS ($P = 0.27$; HR, 0.996), irrespective of the treatment arm. As would be expected, however, OS was influenced by age ($P = 0.025$; HR, 1.013).

The subgroup analysis showed that the absolute difference in DFS at 3 years was maintained in all age groups, including patients aged ≥ 70 years (65% with capecitabine vs. 61% with 5-FU/LV; Figure 2). Furthermore, there was a consistent

Figure 4 Most Common Treatment-Related Adverse Events in Elderly Patients



All grades, patients aged ≥ 70 years; n = 391.

trend for benefit with capecitabine compared with 5-FU/LV in patients aged ≥ 70 years and < 70 years (Figure 2).

Patients aged ≥ 70 years experienced higher rates of toxicity than younger patients in both treatment arms; however, the safety advantages of capecitabine versus 5-FU/LV were preserved in the older patient group. The overall rate of grade 3/4 treatment-related AEs in patients ≥ 70 years was similar in the capecitabine and 5-FU/LV treatment arms (48% vs. 42%). Patients aged ≥ 70 years experienced less all-grade treatment-related diarrhea, nausea, vomiting, stomatitis, and neutropenia with capecitabine than 5-FU/LV, but more hand-foot syndrome (Figure 4). In addition, both treatment regimens were associated with similar rates of grade 3/4 treatment-related diarrhea (16% with capecitabine vs. 11% with 5-FU/LV), nausea (2% vs. 2%), and vomiting (2% vs. 1%). However, a lower rate of grade 3/4 treatment-related stomatitis (3% vs. 21%) and neutropenia (3% vs. 7%) was reported with capecitabine versus 5-FU/LV, whereas a higher rate of grade 3 treatment-related hand-foot syndrome was observed with capecitabine (22% vs. 0).

Economic Evaluation

Survival data and details of medical resource utilization from the X-ACT trial have allowed the cost effectiveness of capecitabine relative to 5-FU/LV to be evaluated in the adjuvant setting. To date, pharmacoeconomic analyses have been completed in the United Kingdom,[19] United States,[20,21] Italy,[22] France,[23] and Portugal.[24] The UK and US analyses are considered here in detail.[19,21]

For these analyses, a health-state transition model was developed to estimate incremental cost impact and effectiveness in terms of relapse-free months or life months (LMs) using survival data from the X-ACT trial. Quality-adjusted LMs (QALMs) gained, in which QALMs are a measure of the time spent in each health state weighted by a utility, were used in some of the

Table 6 Direct and Indirect Costs During Adjuvant Therapy for Colon Cancer: UK and US Scenarios[19,21]

Type of Cost	United Kingdom (£)			United States ($)		
	Capecitabine	5-FU/LV	Net Cost Savings	Capecitabine	5-FU/LV	Net Cost Savings
Direct Medical Costs						
Drug acquisition	2081	602	–1479	10,174	83	–10,091
Visits for study drug administration	419	5151	4732	556	9237	8681
Hospital use	399	459	60	1895	2183	288
Physician consultations for AEs	154	145	–9	142	132	–11
Medications for treating AEs	86	345	259	124	310	186
Hospital transport service	38	126	88	Not available	Not available	Not available
Subtotal	**3177**	**6828**	**3651**	**12,891**	**11,944**	**–947**
Indirect Costs						
Time for travel	319	1503	1184	689	3297	2607
Travel	62	196	134	120	395	275
Total	**3558**	**8527**	**4969**	**13,701**	**15,636**	**1935**

analyses. Utility values for the various health states were taken from the published literature.[25] The X-ACT trial included very few patients from North America (< 2%), so the US economic analyses are based on US costs but consider outcomes in a predominantly non-US population.

The model consisted of 3 health states: stable (disease and relapse free), postrelapse, and death, with further subclassification of the postrelapse category into relapse (ie, during subsequent treatment for metastatic colon cancer), remission, and the 12-month period before death. A relapse event was defined as instance of relapse, new colon cancer, or death from colon cancer or treatment. The time spent in each health state was estimated by extrapolating the RFS and OS data from the X-ACT trial to a lifetime horizon.

Unit costs for drug administration, hospitalizations, consultations, AE medications, and patient time were estimated from local published sources. Costs relating to the posttreatment period (ie, prerelapse and postrelapse maintenance, relapse, and palliative care) were based on available literature.[26-28] Patient time costs and travel expenses during the trial period were also analyzed to assess the impact of oral versus I.V. administration on this dimension. Further details of the model and the assumptions made are described by Cassidy et al.[19]

Capecitabine Acquisition Costs are Offset by 5-FU/LV Administration Costs

Direct and indirect costs associated with capecitabine and 5-FU/LV when used as adjuvant therapy in the United States and United Kingdom are presented in Table 6.[19,21] In both countries, although the mean cost of chemotherapy per patient was higher in the capecitabine arm, the mean number of treatment administration visits was almost 4-fold lower than with 5-FU/LV (7.4 visits vs. 28 visits in 6 months). This resulted in higher costs for drug administration for 5-FU/LV compared with capecitabine (Table 6). Therefore, the higher acquisition cost of capecitabine is partially or completely offset, depending on the country, by savings in drug administration costs compared with 5-FU/LV (Table 6).

Capecitabine Has Lower Adverse Event–Related Costs Than 5-FU/LV

The improved safety profile of capecitabine compared with 5-FU/LV was also reflected in the need for fewer costly medications for the management of treatment-related AEs. In particular, capecitabine reduced the need for fluconazole for stomatitis, 5-HT_3 antagonists for nausea/vomiting, and cytokines for neutropenia. Overall, the mean cost of medications per patient for the management of AEs was consistently lower in the capecitabine arm than in the 5-FU/LV arm (Table 6).

The mean number of physician visits because of AEs was similar in each treatment arm (1.93 and 1.92 for capecitabine and 5-FU/LV, respectively). However, there were 16% fewer AE-related hospital admissions and 15% fewer days spent in a hospital with capecitabine versus 5-FU/LV (10.6 admissions and 12.8 admissions, respectively, and 113 and 130 days, respectively). Consequently, the mean cost of hospitalizations was lower with capecitabine than with 5-FU/LV, although the cost of physician consultations was similar in both treatment groups (Table 6).

Capecitabine Reduces Patient Travel and Time Versus 5-FU/LV

The need for travel to the clinic is markedly reduced through the use of capecitabine versus the Mayo Clinic 5-FU/LV regimen. A projected mean of 27 hours per patient were required for travel in patients receiving capecitabine compared with 125 hours with 5-FU/LV with associated reductions in travel-related time and costs (Table 6).

Capecitabine is a Dominant Strategy Versus 5-FU/LV in the Adjuvant Setting

Total cost data from the United States and the United Kingdom show that capecitabine saves costs from a societal per-

spective compared with 5-FU/LV in the adjuvant setting when costs during treatment are considered (Table 6). This remains true when costs are estimated for a projected lifetime; the lifetime cost savings with capecitabine versus 5-FU/LV are £4969 per patient in the United Kingdom and US $1935 per patient in the United States.[19,21]

According to the model, capecitabine is also projected to increase life expectancy versus 5-FU/LV. In terms of OS, the Kaplan-Meier projection shows that 81.3% of patients receiving capecitabine would survive at 36 months compared with 77.6% of patients receiving 5-FU/LV, an absolute difference of 3.7%. According to the model, the projected survival gains with capecitabine over a lifetime are 8.4 LMs and 9 QALMs.

Therefore, in economic terms, capecitabine is a "dominant" (ie, less expensive and more effective) treatment strategy relative to 5-FU/LV in the adjuvant setting.

Discussion

Steady improvements made over the past 15 years in the adjuvant treatment of colon cancer mean that > 80% of patients can now expect to survive for ≥ 4 years after diagnosis.[29] This compares with a 4-year survival rate of < 60% for patients who were treated with surgery alone before the benefits of adjuvant therapy were recognized.[30] It is unlikely, however, that the incremental gains made in the adjuvant setting are going to stop in the near future as ongoing trials continue to refine our understanding of how best to treat this type of cancer.

The X-ACT trial leads us one more step along this path.[12] The trial confronts the important issue of whether or not I.V. 5-FU/LV can be replaced by the oral fluoropyrimidine capecitabine. By demonstrating convincingly that capecitabine is at least as effective as I.V. bolus 5-FU/LV in terms of 3-year DFS, that it is associated with fewer grade 3/4 AEs, that it reduces toxicity-related hospitalizations, and that it is more convenient for patients and physicians, the X-ACT trial shows that capecitabine can indeed replace 5-FU/LV as adjuvant therapy in patients with stage III disease.

As an extension of the X-ACT trial, resource data show that capecitabine reduces visits to the clinic and the medical resources required for managing AEs.[19] From a societal perspective, the lifetime savings associated with these benefits are approximately £5000[19] and $2000 per patient[21] compared with 5-FU/LV. These benefits also extend to health-care providers, such as the UK National Health Service, because the savings in direct costs associated with the use of capecitabine versus 5-FU/LV easily offset the higher acquisition cost of capecitabine. By projecting the survival benefits of capecitabine from the X-ACT trial to the lifetime of a patient, collectively these data suggest that capecitabine is a dominant strategy (ie, less costly and more effective) for the adjuvant therapy of colon cancer versus 5-FU/LV.

Another important finding from the X-ACT trial is that the efficacy and safety benefits of capecitabine relative to 5-FU/LV extend to patients aged ≥ 70 years, who constitute a major proportion of those diagnosed with colon cancer. This is an age group that is commonly overlooked in clinical trials and, as a result, is often undertreated despite the proven efficacy of adjuvant therapy.[31,32] The findings of the X-ACT trial add to the growing volume of evidence suggesting that age alone should not be a barrier to the use of adjuvant chemotherapy in colon cancer.[33,34] Rather, performance status (PS) should be the governing factor. In addition, it is important to remember that renal impairment is more common in older patients and is associated with an increased risk of toxicity with bolus 5-FU/LV or capecitabine. Renal function should, therefore, be checked before starting treatment. Importantly, capecitabine dose modifications have been defined for patients with renal impairment.[14]

Table 7 Three-Year DFS in Patients with Stage III Colon Cancer Treated with Adjuvant Therapy

Trial	5-FU Schedule	3-Year DFS (%)	Hazard Ratio (95% CI)	Absolute Difference in 3-Year DFS (%)
X-ACT				
5-FU/LV	Bolus	60.6	0.87 (0.75-1)	3.6
Capecitabine	Oral	64.2		
MOSAIC				
5-FU/LV	Infusion	65.3	0.76 (0.62-0.92)	6.9
5-FU/LV and oxaliplatin	Infusion	72.2		
NSABP C-07				
5-FU/LV	Bolus	65.5	0.77 (0.65-0.92)	6.7
5-FU/LV and oxaliplatin	Bolus	72.2		
PETACC-3				
5-FU/LV	Infusion	59.9	0.89 (0.77-1.03)	3
5-FU/LV and irinotecan	Infusion	62.9		

Abbreviations: MOSAIC = Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer; NSABP = National Surgical Adjuvant Breast and Bowel Project; PETACC = Pan-European Trial for Adjuvant Treatment of Colon Cancer

In the metastatic setting, multi-agent rather than single-agent therapy has become the standard of care for patients with CRC. This generally involves the use of a fluoropyrimidine in combination with oxaliplatin or irinotecan and, more recently, plus the anti–vascular endothelial growth factor antibody bevacizumab, when it is available. Rapid progress is being made to extend the benefits of these regimens to the adjuvant setting. The recently completed MOSAIC (Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer)[35] and NSAPB (National Surgical Adjuvant Breast and Bowel Project) C-07[36] trials show that adding oxaliplatin to infused or bolus regimens of 5-FU/LV improves 3-year DFS compared with 5-FU/LV alone in patients with stage II/III disease. In contrast, studies with irinotecan added to 5-FU/LV in patients with stage III disease have failed to demonstrate any superiority of combination therapy over 5-FU/LV alone.[37,38] Available data from these trials and the X-ACT trial are presented in Table 7.

Capecitabine has the potential to replace 5-FU/LV in combination regimens in the adjuvant setting. Although studies with multi-agent adjuvant regimens involving capecitabine are cur-

rently in progress, extensive experience in the metastatic setting now shows that capecitabine is an ideal backbone for combination regimens with other cytotoxic agents and with novel targeted agents such as bevacizumab. For example, XELOX, a combination regimen in which oxaliplatin 130 mg/m^2 is administered as a single dose on day 1 followed by capecitabine 1000 mg/m^2 twice daily on days 1-15, every 21 days, has been shown to be an effective and well-tolerated alternative to 5-FU/LV in metastatic disease.[39-41] The addition of bevacizumab to XELOX has also demonstrated promising results with an acceptable tolerability profile in metastatic disease.[42] Recently, preliminary analysis of the XELOX-1 trial, a randomized 2 × 2 factorial phase III comparison of XELOX versus FOLFOX4 (5-FU/LV/oxaliplatin) with or without bevacizumab or placebo was presented.[43] XELOX was shown to be noninferior to FOLFOX4 in terms of PFS. Bevacizumab was shown to add clinically and statistically significant benefit to oxaliplatin-based chemotherapy. Finally, the comparable safety of the XELOX regimen versus I.V. 5-FU/LV has recently been confirmed in the adjuvant setting.[44]

Although there are increasing indications that multiagent therapy offers survival gains in the adjuvant setting, it is quite possible that such intensive therapy might not be appropriate for all patients. Selection of therapy is likely to involve an assessment of the risk-benefit profile of available adjuvant regimens by the physician and the patient, with age, disease stage, PS, comorbidities, and patient preference likely to be moderating factors dictating the final choice. Although the magnitude of the DFS benefit is important for patients, it must be balanced against the adverse effects of adding more drugs, such as oxaliplatin, to the regimen. With this in mind, the availability of an orally administered chemotherapy, such as capecitabine, is likely to increase the options available to patients.

Patients with stage II colon cancer were not included in the X-ACT study because, at the time the study was planned, there was no consensus that patients with stage II tumors should receive adjuvant therapy. However, recent reports document a small but consistent therapeutic benefit with fluorouracil-based treatment in patients with stage II disease.[45-47] Because the absolute survival benefit associated with adjuvant therapy in this patient group is small (approximately 1%-5%), the risks associated with chemotherapy need to be minimized. Because of the favorable risk-to-benefit ratio of capecitabine demonstrated in the X-ACT trial, capecitabine should be considered as a potential treatment option in this patient group.

Finally, these results should be viewed in the context of emerging data that there are geographic variations in the tolerability of fluoropyrimidines.[48] Specifically, patients from the United States appear to have a higher incidence of fluoropyrimidine-related toxicities than those from the rest of the world. The reason for this is unclear, but importantly, this difference in tolerability is seen for 5-FU/LV and capecitabine. Although a specific analysis of efficacy, tolerability, and economic evaluation cannot be performed for patients in the United States, available data would indicate that differences in tolerability among US patients should apply to both treatment arms of the X-ACT study. Nevertheless, many US clinicians tend to use a starting dose of 1000 mg/m^2 of capecitabine daily for 14 days on the basis of their clinical experience. As ever, it is also important that capecitabine treatment is interrupted and subsequent doses modified in patients developing toxicity of grade ≥ 2.

Conclusion

The X-ACT trial convincingly demonstrates that, on the basis of efficacy, safety, convenience, and cost, capecitabine offers at least equivalent clinical benefit compared with bolus 5-FU/LV in the adjuvant treatment of stage III colon cancer and should replace I.V. 5-FU/LV in this setting. The favorable benefit-to-risk ratio offered by capecitabine might also lead to higher rates of acceptance of adjuvant therapy among patients who would have previously considered the benefits of treatment too marginal, for example, those with stage II disease or patients with a suboptimal PS. By providing compelling evidence for the efficacy of capecitabine, the X-ACT trial has not only helped to better define the role of capecitabine but has also broadened the options available to patients with early-stage disease to include a uniquely effective oral outpatient treatment.

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