Supplementary appendix

Supplement to: Schmoll H-J, Twelves C, Sun W, et al. Effect of adjuvant capecitabine or fluorouracil, with or without oxaliplatin, on survival outcomes in stage III colon cancer and the effect of oxaliplatin on post-relapse survival: a pooled analysis of individual patient data from four randomised controlled trials.

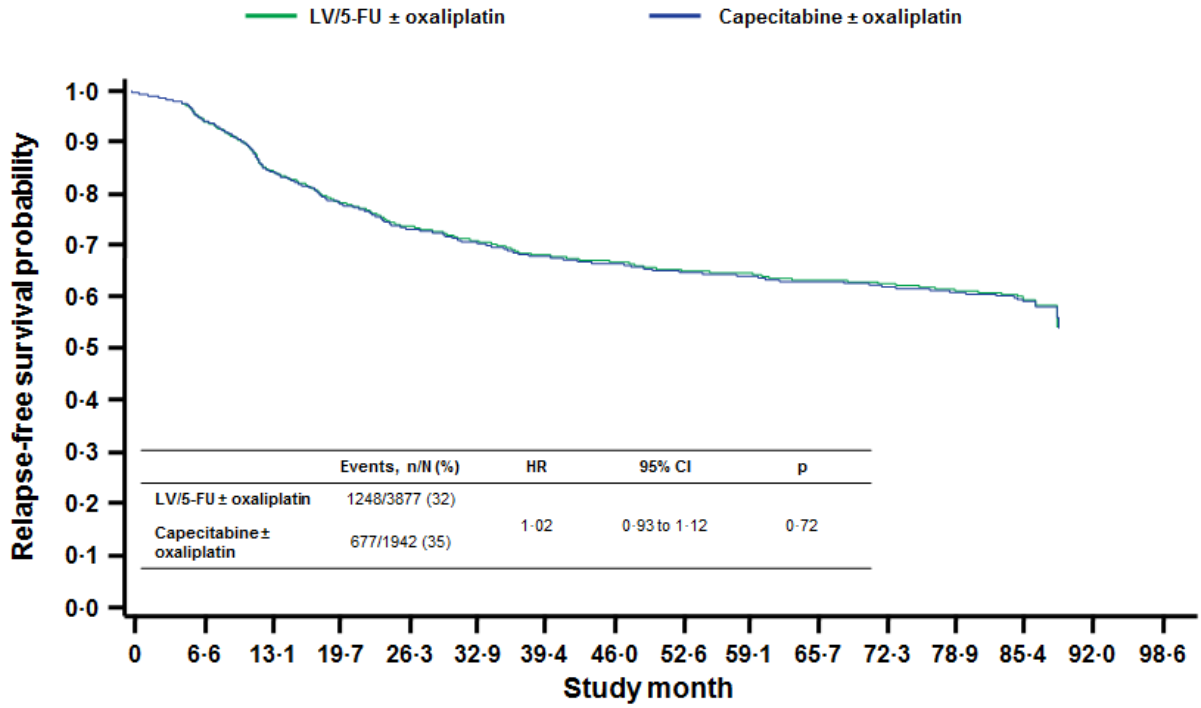
Appendix 1: Further study details

	X-ACT[8]	XELOXA[7]	NSABP C-08[14]	AVANT[15]
Disease setting	Histologically confirmed stage III colon carcinoma	Histologically confirmed stage III colon carcinoma (T1-4/N1-2/M0), defined as a tumour located 15 cm from the anal verge or above the peritoneal reflection	Stages II and III colon adenocarcinoma	Histologically confirmed stage III or high-risk stage II colon carcinoma
Age range for eligibility	18–75	≥18	Not stated	≥18
Disease evaluation method	Abdominal and pelvic CT or MRI and either thoracic radiography or thoracic CT or MRI	Abdominal CT, MRI, or ultrasound and chest x-rays	Not stated	Abdominal and pelvic CT/MRI or ultrasound, and chest CT or MRI or radiograph Suspicious lesions were detected by ultrasound or chest radiograph and required confirmation by CT or MRI
Permitted performance status	ECOG 0 or 1	ECOG 0 or 1	ECOG 0 or 1	Not stated
Previous treatments permitted	Surgery	Surgery	Surgery	Surgery
Planned doses/cycles	Twenty-four weeks of either eight cycles of capecitabine (1250 mg/m^2, twice daily on days 1–14 every 21 days), or six cycles of LV (20 mg/m^2)/5-FU (425 mg/m^2) on days 1–5 every 28 days	XELOX: oxaliplatin (130 mg/m^2 on day 1) and capecitabine (1000 mg/m^2 twice daily on days 1–14) of a 3-week cycle for eight cycles LV/5-FU: 20 mg/m^2 LV and 425 mg/m^2 5-FU on days 1–5, repeated at 4 weeks, 8 weeks, and every 5 weeks, for a total of six courses (Mayo Clinic regimen); or 500 mg/m^2 LV and 500 mg/m^2 5-FU, repeated six times weekly, followed by a 2-week rest period, for a total of four 8-week courses (Roswell Park regimen)	mFOLFOX-6: 400 mg/m^2 LV on day 1, 400 mg/m^2 bolus 5-FU on day 1 followed by 2400 mg/m^2 over 46 hours, and 85 mg/m^2 oxaliplatin on day 1 Bevacizumab: 5 mg/kg on day 1 All therapy was given every 2 weeks for 12 (mFOLFOX-6) or 26 doses (bevacizumab)	FOLFOX-4: 85 mg/m² oxaliplatin, 200 mg/m² LV, and 400 mg/m² bolus then 600 mg/m² continuous infusion 5-FU on day 1; 200 mg/m² LV, 400 mg/m² bolus then 600 mg/m² continuous infusion 5-FU on day 2 Cycles were repeated every 2 weeks for 12 cycles XELOX: 130 mg/m² oxaliplatin on day 1 every 3 weeks and capecitabine (1000 mg/m² twice daily with first dose in the evening of day 1 and last dose in the

				morning of day 15) every 3 weeks for eight cycles Bevacizumab: 5 mg/kg with FOLFOX-4 on day 1 or 7·5 mg/kg with XELOX on day 1, then 7·5 mg/kg every 3 weeks for a further eight cycles

5-FU, 5-fluorouracil; AVANT, Avastin Adjuvant ; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FOLFOX, leucovorin, 5-fluorouracil plus oxaliplatin; LV, leucovorin; mFOLFOX-6, modified FOLFOX-6; MRI, magnetic resonance imaging; NSABP, National Surgical Adjuvant Breast and Bowel Project; X-ACT, Xeloda in Adjuvant Colon Cancer Therapy; XELOX, capecitabine plus oxaliplatin; XELOXA, XELOX in Adjuvant Colon Cancer Treatment.

Appendix 2: **Adjusted survival curves of relapse-free survival for capecitabine ± oxaliplatin and leucovorin/5-fluorouracil ± oxaliplatin, adjusted for gender, age, T-stage, and N-stage**



5-FU, 5-fluorouracil; LV, leucovorin.

Appendix 3: **Capecitabine ± oxaliplatin versus LV/5-FU ± oxaliplatin sensitivity analyses: number of lymph nodes examined**

		HR	95% CI	p-value
Disease-free survival				
	≤12 lymph nodes examined	0·91	0·75–1·10	0·33
	>12 lymph nodes examined	1·03	0·86–1·23	0·76
Relapse-free survival				
	≤12 lymph nodes examined	0·88	0·72–1·08	0·21
	>12 lymph nodes examined	1·04	0·86–1·24	0·71
Overall survival				
	≤12 lymph nodes examined	0·98	0·78–1·23	0·85
	>12 lymph nodes examined	1·04	0·84–1·30	0·70

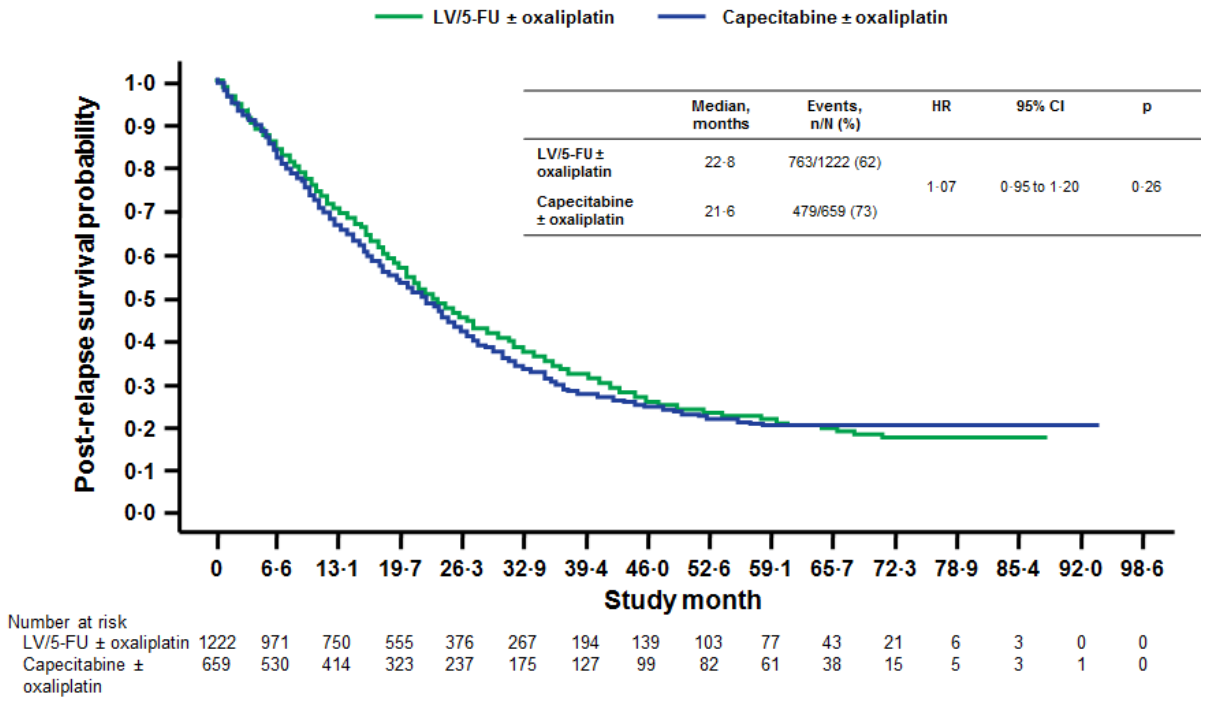
5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; LV, leucovorin.

Appendix 4: **Sensitivity analyses of effects of study entry date (2004 or later versus before 2004)**

	HR	95% CI	p-value
Capecitabine ± oxaliplatin versus LV/5-FU ± oxaliplatin			
Disease-free survival	0·92	0·84–1·01	0·094
Relapse-free survival	0·92	0·83–1·01	0·090
Overall survival	0·94	0·84–1·05	0·28
Post-relapse survival	1·02	0·88–1·19	0·79
XELOX versus capecitabine monotherapy			
Disease-free survival	0·67	0·53–0·86	0·0015
Relapse-free survival	0·67	0·52–0·87	0·0022
Overall survival	0·69	0·52–0·91	0·0083
Post-relapse survival	0·92	0·67–1·25	0·59
XELOX/FOLFOX versus LV/5-FU			
Post-relapse survival	1·02	0·88–1·19	0·79

5-FU, 5-fluorouracil; CI, confidence interval; FOLFOX, leucovorin, 5-fluorouracil plus oxaliplatin; HR, hazard ratio; LV, leucovorin; XELOX, capecitabine plus oxaliplatin.

Appendix 5: **Unadjusted Kaplan–Meier plot of post-relapse survival in patients receiving adjuvant capecitabine ± oxaliplatin versus leucovorin/5-fluorouracil (5-FU/LV) ± oxaliplatin**

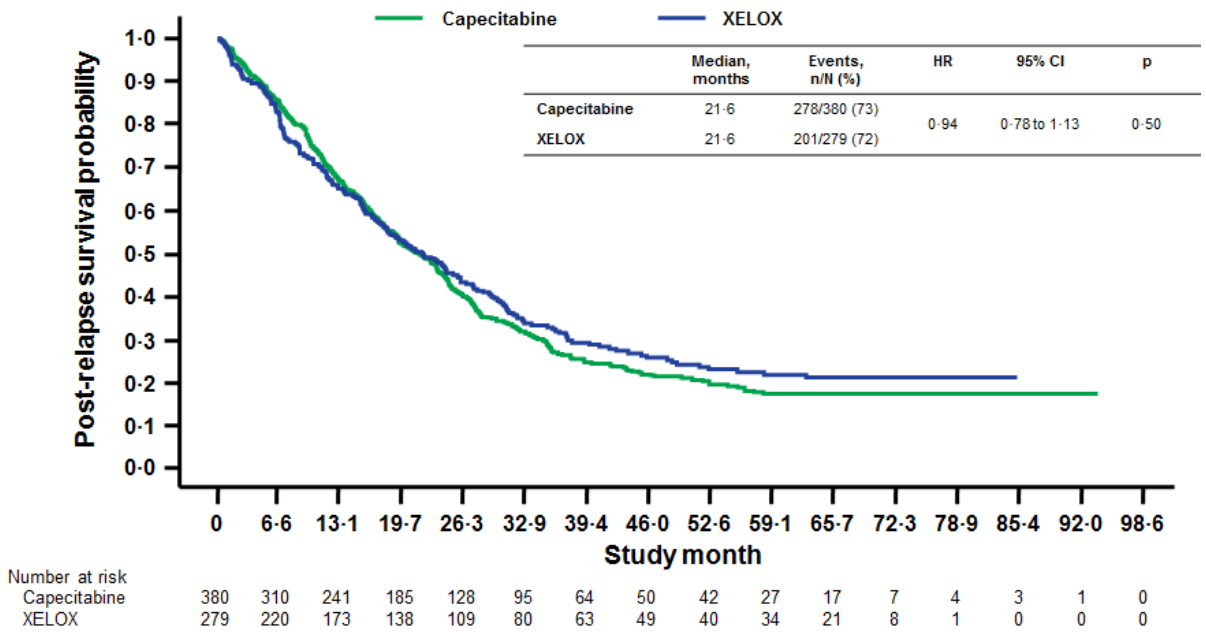


Number at risk

LV/5-FU ± oxaliplatin	1222	971	750	555	376	267	194	139	103	77	43	21	6	3	0	0
Capecitabine ± oxaliplatin	659	530	414	323	237	175	127	99	82	61	38	15	5	3	1	0

5-FU, 5-fluorouracil; LV, leucovorin.

Appendix 6: **Unadjusted Kaplan–Meier plot of post-relapse survival in patients receiving adjuvant capecitabine plus oxaliplatin (XELOX) versus capecitabine alone**



XELOX, capecitabine plus oxaliplatin.

Appendix 7: **Impact of time from surgery on post-relapse survival**

Overall population				
	<1 year (N=418)		**≥1 year (N=1083)**	
Patients with event, n (%)	347 (83·0)		617 (57·0)	
Median time to event, days (range)	445 (5–2691)		818 (1–2691)	
HR (95% CI)	0·56 (0·49–0·64)			
p-value	<0·0001			
LV/5-FU *vs* oxaliplatin-based therapy				
	<1 year		**≥1 year**	
	LV/5-FU (N=211)	**XELOX/FOLFOX-4/mFOLFOX-6 (N=207)**	**LV/5-FU (N=533)**	**XELOX/FOLFOX-4/mFOLFOX-6 (N=550)**
Patients with event, n (%)	188 (89·1)	159 (76·8)	362 (67·9)	255 (46·4)
Median time to event, days (range)	479 (6–2691)	360 (5–2590)	788 (1–2691)	861 (1–2325)
HR (95% CI)	1·08 (0·87–1·33)		0·88 (0·75–1·04)	
p-value	0·50		0·12	

5-FU, 5-fluorouracil; CI, confidence interval; FOLFOX, leucovorin, 5-fluorouracil plus oxaliplatin; HR, hazard ratio; LV, leucovorin; XELOX, capecitabine plus oxaliplatin.