Supplementary Online Content

Yoshino T, Yamanaka T, Oki E, et al. Efficacy and long-term peripheral sensory neuropathy of 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: the ACHIEVE phase 3 randomized clinical trial. Published online Spetember 12, 2019. doi:10.1001/jamaoncol.2019.2572

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

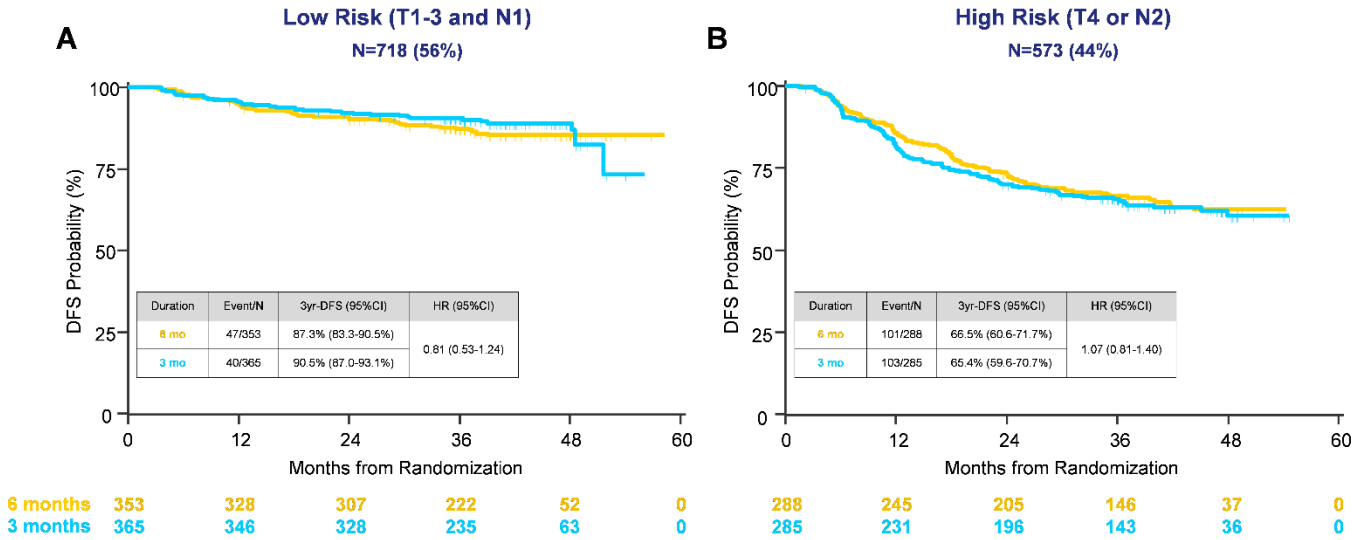
Patient inclusion and exclusion criteria

Patients were eligible for inclusion if they were aged ≥20 years, and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, primary cancer of the caecum, colon, or rectosigmoid (diagnosed from operative findings and examination of the resected specimen), a complete curative resection including D2 or D3 lymphadenectomy, stage III disease (Tumour stage [T] any, Node [N]1/2/3, Metastases [M] 0), and adequate vital organ function (neutrophil count 1,500/mm^3, platelet count 100,000/mm^3, serum creatinine 1.5 times the upper limit of normal [ULN], creatinine clearance [CCr, calculated using Cockcroft-Gault equation value] ≥ 30 mL/min, total bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤ 100 IU/L, and carcinoembryonic antigen (CEA) ≤ 10 ng/mL). Exclusion criteria were: cancer of the appendix, a history of another malignancy, PSN of grade 1 or higher, and a history of prior treatment with oxaliplatin. Eligible patients had to be enrolled into the trial within 8 weeks of surgery. Patient enrolment and data collection were managed using an electronic data capturing system.

Protocol Amendment

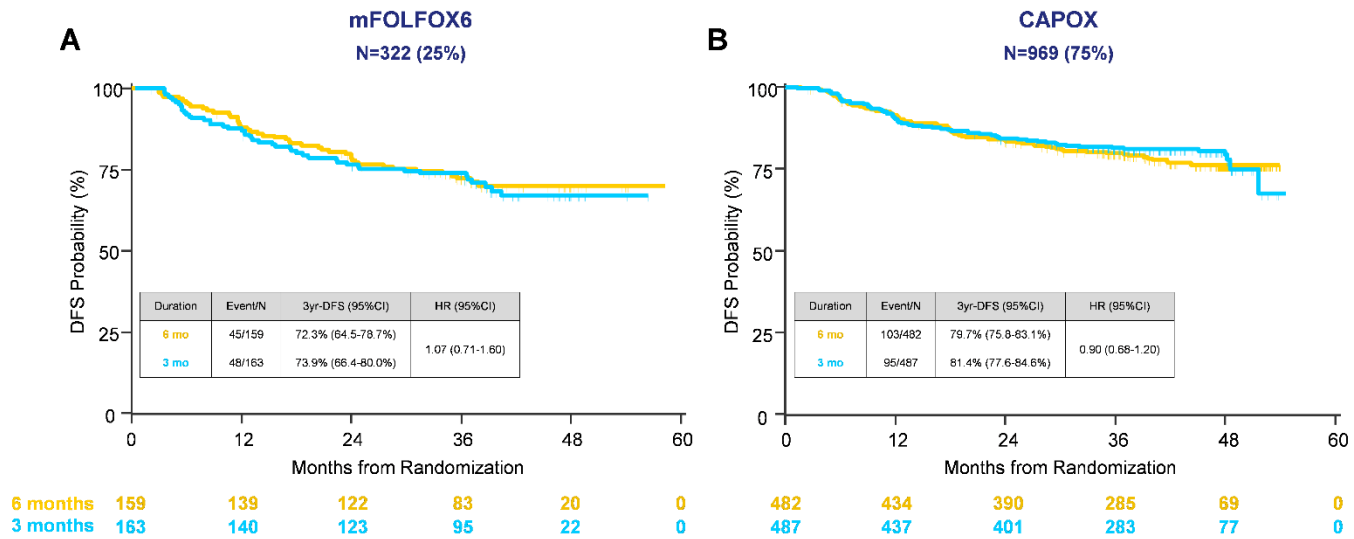
Data monitoring during the study period revealed that the discontinuation of CAPOX therapy was more frequent than expected. Thus, the protocol was amended to include creatinine clearance (CCr) ≥ 30 mL/min as an eligibility criterion. CAPOX therapy was also initiated with a lower dose of capecitabine (1,500 mg/m2 per day) when patients had a CCr of 30-50 mL/min and/or an age ≥ 70 years old. One patient with a CCr < 30 mL/min was enrolled in this study. After the date of the protocol amendment, October 25, 2013, 99 patients receiving CAPOX started the treatment with a lower dose of capecitabine.

eFigure 1. DFS According to Whether Patients Were Classified as Having Low-risk or High-risk Disease



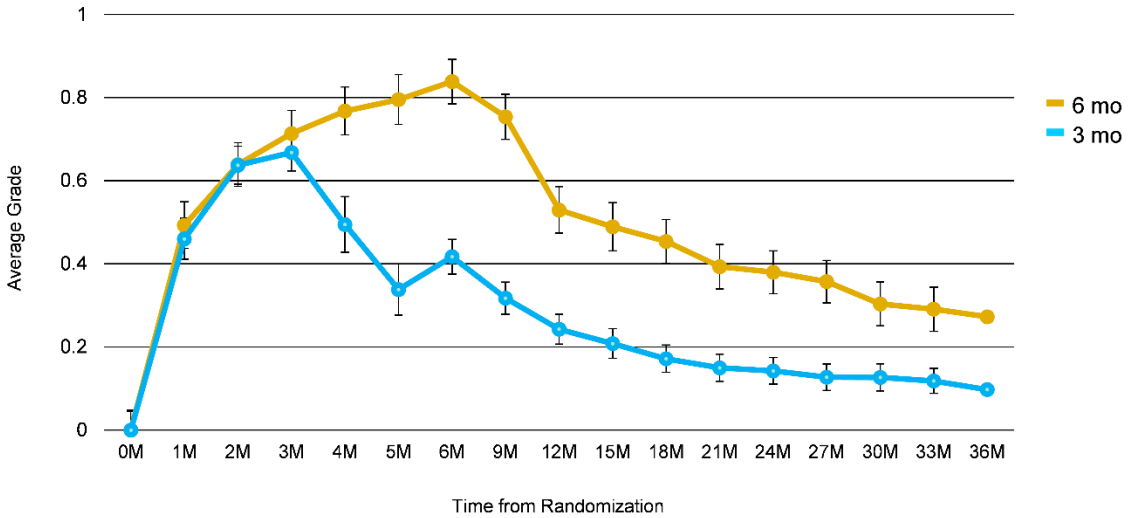
(A) Three-year DFS rate in low-risk (T1 to 3 and N1) patients treated with adjuvant chemotherapy for 6 months or 3 months, (B) Three-year DFS rate in high-risk (T4 or N2) patients treated with adjuvant chemotherapy for 6-months or 3-months. CI indicates confidence interval; DFS, disease-free survival; HR, hazard ratio; mo, month; N, number of patients, yr, year.

eFigure 2. DFS According to Regimen Used



Three-year DFS rates for patients treated for 3 months *v* 6 months with mFOLFOX6 (A) or CAPOX (B) regimen. CAPOX indicates capecitabine plus oxaliplatin; CI indicates confidence interval; DFS, disease-free survival; mFOLFOX6, modified 5-fluorouracil, *l*-leucovorin and oxaliplatin; HR, hazard ratio; mo, month; N, number of patients; yr, year.

eFigure 3. PSN by Treatment Duration



Patients reported PSN using CTCAE ver4. Vertical axis shows the average of PSN grade according to CTCAE ver4 at each time point. Blue, 6 months of adjuvant treatment; red, 3 months of adjuvant treatment. CTCAE indicates Common Terminology Criteria for Adverse Events; PSN, peripheral sensory neuropathy.

eTable 1. Time Course of Occurrence and Recovery from HFS

		Total			
		During Trt	**≤12mo**	**≤24mo**	**≤36mo**
3mo therapy	**Total N**	650	634	460	380
	Grade 3	4 (0.6)	2 (0.3)	0 (0)	0 (0)
	Grade 2	33 (5)	0 (0)	0(0)	0 (0)
	Grade 1	180 (28)	16 (3)	7 (2)	4 (1)
	Grade 0	433 (67)	616 (97)	453 (99)	376 (99)
6mo therapy	**N**	641	589	427	363
	Grade 3	15 (2)	0 (0)	0 (0)	0 (0)
	Grade 2	59 (9)	1(0.2)	0 (0)	0 (0)
	Grade 1	205 (32)	42 (7)	12 (3)	11 (3)
	Grade 0	362 (57)	546 (93)	415 (97)	352 (97)

Time course of occurrence and recovery from HFS in patients receiving 3 months or 6 months of adjuvant chemotherapy. mo indicates months; HFS, hand-foot syndrome; N, number of patients; Trt, treatment.