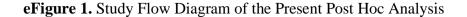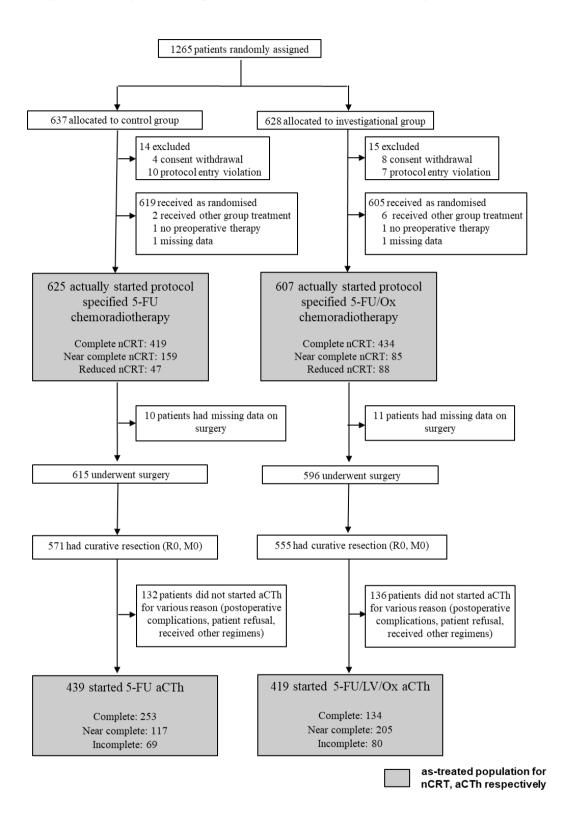# Supplementary Online Content

Diefenhardt M, Ludmir EB, Hofheinz R-D, et al. Association of treatment adherence with oncologic outcome for patients with rectal cancer: a post hoc analysis of the CAO/ARO/AIO-04 phase 3 randomized clinical trial. *JAMA Oncol.* Published online July 9, 2020. doi:10.1001/jamaoncol.2020.2394

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

eFigure 1. Study Flow Diagram of the Present Post Hoc Analysis

1265 patients randomly assigned

637 allocated to control group

628 allocated to investigational group

14 excluded
  4 consent withdrawal
  10 protocol entry violation

15 excluded
  8 consent withdrawal
  7 protocol entry violation

619 received as randomised
  2 received other group treatment
  1 no preoperative therapy
  1 missing data

605 received as randomised
  6 received other group treatment
  1 no preoperative therapy
  1 missing data

625 actually started protocol specified 5-FU chemoradiotherapy

Complete nCRT: 419
Near complete nCRT: 159
Reduced nCRT: 47

607 actually started protocol specified 5-FU/Ox chemoradiotherapy

Complete nCRT: 434
Near complete nCRT: 85
Reduced nCRT: 88

10 patients had missing data on surgery

11 patients had missing data on surgery

615 underwent surgery

596 underwent surgery

571 had curative resection (R0, M0)

555 had curative resection (R0, M0)

132 patients did not started aCTh for various reason (postoperative complications, patient refusal, received other regimens)

136 patients did not started aCTh for various reason (postoperative complications, patient refusal, received other regimens)

439 started 5-FU aCTh

Complete: 253
Near complete: 117
Incomplete: 69

419 started 5-FU/LV/Ox aCTh

Complete: 134
Near complete: 205
Incomplete: 80

as-treated population for nCRT, aCTh respectively

eTable 1. Association of Patient Characteristics With the Compliance to nCRT in the Two Treatment Groups

| Characteristics | | No. | 5-FU treatment group N=625 | | | | No. | 5-FU/Ox treatment group N=607 | | | |
			complete nCRT	near complete nCRT	reduced nCRT	P-value		complete nCRT	near complete nCRT	reduced nCRT	P-value
Number (%)		625	419 (67.0%)	159 (25.4%)	47 (7.5%)		607	434 (71.5%)	85 (14.0%)	88 (14.5%)	
Age											
< 70 years		470	326 (69.4%)	108 (23.0%)	36 (7.7%)		465	338 (72.7%)	67 (14.4%)	60 (12.9%)	
≥ 70 years		155	93 (60.0%)	51 (32.9%)	11 (7.1%)	**0.048**	142	96 (67.6%)	18 (12.7%)	28 (19.7%)	0.13
Gender											
Male		442	295 (66.7%)	120 (27.1%)	27 (6.1%)		430	322 (74.9%)	56 (13.0%)	52 (12.1%)	
Female		183	124 (67.8%)	39 (21.3%)	20 (10.9%)	0.06	177	112 (69.3%)	29 (16.4%)	36 (20.3%)	**0.01**
ECOG											
Grade 0		415	328 (79.0%)	121 (25.4%)	28 (5.9%)		479	348 (72.7%)	66 (13.8%)	65 (13.6%)	
Grade 1		158	80 (61.1%)	35 (26.7%)	16 (12.2%)		115	77 (67.0%)	19 (16.5%)	19 (16.5%)	
Grade 2		45	7 (70.0%)	2 (20.0%)	1 (10.0%)	0.14	6	4 (66.7%)	0 (0%)	2 (33.3%)	0.42
BMI [kg/m²]											
underweight 0-18.49		9	7 (77.8%)	1 (11.1%)	1 (11.1%)		8	3 (37.5%)	1 (12.5%)	4 (50.0%)	
normal weight 18.5-24.9		196	138 (70.4%)	44 (22.4%)	14 (7.1%)		211	146 (69.2%)	27 (12.8%)	38 (18.0%)	
Overweight 25-29.9		280	189 (67.5%)	67 (23.9%)	24 (8.6%)		258	196 (76.0%)	34 (13.2%)	28 (10.9%)	
Obese ≥30		140	85 (60.7%)	47 (33.6%)	8 (5.7%)	0.25	130	89 (68.5%)	23 (17.7%)	18 (13.8%)	**0.02**
cT											
cT2		32	18 (56.3%)	12 (37.5%)	2 (6.3%)		22	12 (54.5%)	7 (31.8%)	3 (13.6%)	
cT3		540	363 (67.2%)	135 (25.0%)	42 (7.8%)		543	401 (73.8%)	67 (12.3%)	75 (13.8%)	
cT4		49	34 (69.4%)	12 (24.5%)	3 (6.1%)	0.61	41	20 (48.8%)	11 (26.8%)	10 (24.4%)	**0.001**
cN											
cN0		158	99 (62.7%)	42 (26.6%)	17 (10.8%)		145	100 (69.0%)	26 (17.9%)	19 (13.1%)	
cN+		454	309 (68.1%)	116 (25.6%)	29 (6.4%)	0.17	447	321 (71.8%)	59 (13.2%)	67 (15.0%)	0.35
Tumor Differentiation											
G1		31	27 (87.1%)	3 (9.7%)	1 (3.2%)		33	22 (66.7%)	354 (72.2%)	8 (24.2%)	
G2		504	136 (64.7%)	136 (27.0%)	42 (8.3%)		490	3 (9.1%)	69 (14.1%)	67 (13.7%)	
G3		50	34 (68.0%)	13 (26.0%)	3 (6.0%)	0.15	49	8 (24.2%)	9 (18.4%)	7 (14.3%)	0.42
Tumor Localisation											

Low		216	147 (68.1%)	58 (26.9%)	11 (5.1%)		247	175 (70.9%)	29 (11.7%)	43 (17.4%)	
Middle		338	215 (63.6%)	89 (26.3%)	34 (10.1%)		298	208 (69.8%)	50 (16.8%)	40 (13.4%)	
High		64	53 (82.8%)	9 (14.1%)	2 (3.1%)	**0.01**	55	45 (81.8%)	6 (10.9%)	4 (7.3%)	0.11

Abbreviations: nCRT, neoadjuvant chemoradiotherapy; BMI, body mass index; 5-FU, 5-fluorouracil; Ox, oxaliplatin

eTable 2. Univariable Analyses of nCRT Compliance and Pretreatment Characteristics on Disease-Free Survival in 5-FU and 5-FU/Ox Group

Univariable analysis	3-year DFS 5-FU nCRT group				3-year DFS 5-FU/Ox nCRT group		
	HR	95% CI	P-value		HR	95% CI	P-value
nCRT compliance							
Complete / near complete	1.265	0.922-1.737	0.15		1.478	0.966-2.261	0.07
/ reduced	**1.815**	**1.142-2.885**	**0.01**		**1.835**	**1.226-2.746**	**0.003**
Gender							
Male / Female	0.787	0.570-1.086	0.15		1.013	0.719-1.428	0.94
Age							
< 70 years / ≥ 70 years	1.172	0.856-1.606	0.32		**1.613**	**1.149-2.265**	**0.006**
ECOG							
Grade 0 / Grade 1	**1.601**	**1.165-2.199**	**0.004**		**1.796**	**1.257-2.566**	**0.001**
/ Grade 2	2.170	0.889-5.299	0.09		0.937	0.131-6.707	0.95
BMI [kg/m²]							
Underweight / normal weight	0.806	0.253-2.567	0.72		0.516	0.161-1.651	0.27
/ overweight	0.236	0.236-2.359	0.62		0.577	0.182-1.831	0.35
/ obese	0.260	0.260-2.688	0.76		0.419	0.127-1.377	0.15
cT-category							
cT2 / cT3	2.145	0.881-5.223	0.09		0.889	0.392-2.012	0.78
/ cT4	**4.382**	**1.682-11.413**	**0.002**		1.399	0.537-3.640	0.49
cN-category							
cN0 / cN+	0.792	0.581-1.080	0.14		1.260	0.857-1.851	0.24
Grading							
G1 / G2	0.971	0.496-1.902	0.93		0.665	0.348-1.270	0.22
/ G3	1.950	0.906-4.196	0.09		1.185	0.551-2.549	0.66
Tumor Localisation							
Low / Middle	**0.583**	**0.432-0.787**	**<0.001**		1.161	0.833-1.618	0.38
/ High	0.930	0.592-1.461	0.75		1.063	0.594-1.902	0.84

Abbreviations: nCRT, neoadjuvant chemoradiotherapy; 5-FU, 5-fluorouracil; Ox, oxaliplatin; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; Bold printed: significant P<0.05

eFigure 2. Prognostic Significance of Adjuvant Chemotherapy Compliance for Disease-Free Survival Based on Univariable Analysis in Patients That Received the Full Dose of nCRT for (A) Adjuvant 5-FU CT (complete vs near complete P = 0.77; complete vs incomplete P = 0.53) and (B) Adjuvant 5-FU/Ox CT (complete vs near complete P = 0.97; complete vs incomplete P = 0.65). Percentages refer to 3-year DFS [95% confidence interval, CI]).

A — Disease-free survival vs Time [Months]
- complete 5-FU aCTh (82.7% [77.0-88.4])
- near complete 5-FU aCTh (77.9% [68.9-86.9])
- incomplete 5-FU aCTh (85.9% [75.3-96.5])

N risk:
180	169	149	124	72	25	0
84	79	67	55	40	16	0
45	40	38	32	23	14	0

B — Disease-free survival vs Time [Months]
- complete 5-FU/Ox aCTh (84.7% [77.9-91.6])
- near complete 5-FU/Ox aCTh (84.1% [78.0-90.2])
- incomplete 5-FU/Ox aCTh (77.1% [65.5-88.7])

N risk:
111	106	93	80	50	19	0
151	145	131	107	63	33	0
58	52	43	34	24	13	0