Supplementary Appendix

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

Supplement to: Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med 2018;378:1177-88. DOI: 10.1056/NEJMoa1713709

Supplementary Appendices

Supplemental Table 1: Trial-specific design of six international randomized clinical trials within the IDEA collaboration

Trials (Group)	Enrolling countries	Accrual time	Stage	Tumor location	Treatments	Stratification factors	Additional trial-specific comparison
TOSCA (GISCAD)	Italy	06/2007 – 04/2013	Stage III High-risk Stage II	Colon	FOLFOX4 CAPOX	1) Center 2) stage (high-risk stage II vs. III)	FOLFOX4+ bevacizumab vs. FOLFOX4 alone*
SCOT (CACTUS/ OCTO)	UK, Australia, Denmark, Spain, Sweden, New Zealand	05/2008 – 11/2013	Stage III High-risk stage II	Colon Rectum	mFOLFOX6 CAPOX	1) Center 2) T stage (1/2 vs. 3 vs. 4) 3) N stage (1 vs. 2) 4) disease site (Colon vs. Rectum) 5) gender (Male vs. Female) 6) Regimen (mFOLFOX6 vs. CAPOX) 7) initial dose of cap if CAPOX[#]	None
IDEA France (PRODIGE/ GERCOR)	France	05/2009 – 05/2014	Stage III	Colon	mFOLFOX6 CAPOX	1) Center 2) T stage (1/2 vs. 3 vs. 4) 3) N stage (1 vs. 2) 4) age (< 70 vs. >= 70) 5) PS (0 vs. 1 vs. 2)	None
C80702 (CALGB/ SWOG)	USA, Canada	07/2010 – 11/2015	Stage III	Colon	mFOLFOX6	1) N stage (1 vs. 2) 2) low dose aspirin use (yes vs. no)	3 years of celecoxib vs. placebo
HORG (HORG)	Greece	04/2009 – 12/2015	Stage III High-risk stage II	Colon	FOLFOX4 CAPOX	1) center 2) stage (high-risk stage II vs. III) 3) obstruction or perforation (yes vs. no)	None
ACHIEVE (JFMC)	Japan	08/2012 – 06/2014	Stage III	Colon	mFOLFOX6 CAPOX	1) Centers 2) N stage (1 vs. 2) 3) Primary site (colon vs. rectosigmoid vs. multiple) 4) Age (< 70 vs. >= 70) 5) Regimen (mFOLFOX6 vs. CAPOX)	None

[#]Introduced in Feb 2010; *5% of patients in TOSCA received bevacizumab

Supplemental Table 2: TNM Classification of colon cancer by American Joint Committee on Cancer (AJCC), 7th edition

Primary tumor (T)		Lymph nodes (N)		Distant metastasis (M)	
Category	**Description**	**Category**	**Description**	**Category**	**Description**
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M0	No distant metastasis
T1	Tumor invades submucosa	N1	Metastasis in 1-3 regional lymph nodes (metastasis in 1 lymph node: N1a; metastases in 2-3 lymph nodes: N1b)	M1	Distant metastasis (metastasis confined to one organ or site: M1a; metastases in more than one organ/site or the peritoneum
T2	Tumor invades muscularis propria	N2	Metastases in 4 or more regional lymph nodes (metastases in 4-6 lymph nodes: N2a; metastases in 7 or more lymph nodes: N1b)		
T3	Tumor invades through the muscularis propria into pericolorectal tissues				
T4	Tumor penetrates to the surface of the visceral peritoneum (T4a) or invades or is adherent to other organs or structures (T4b)				

Edge SB, Byrd SR, Compton CC, et al., editors. AJCC Cancer Staging Manual. 7th edition Springer-Verlag; New York (NY): 2010. pp. 143–164.

Supplemental Table 3: Patient characteristics by treatment regimen in the IDEA mITT population

Patient characteristics	FOLFOX			CAPOX		
	3 Months (N=3870)	**6 Months** (N=3893)	**Total** (N=7763)	**3 Months** (N=2554)	**6 Months** (N=2517)	**Total** (N=5071)
Age, years						
Median (Range)	64.0 (20, 87)	64.0 (19, 88)	64.0 (19, 88)	65.0 (25, 84)	65.0 (18, 85)	65.0 (18, 85)
Missing	0	2	2	0	0	0
Gender, n (%)						
Male	2170 (56.1%)	2173 (55.8%)	4343 (56.0%)	1468 (57.5%)	1432 (56.9%)	2900 (57.2%)
Female	1699 (43.9%)	1720 (44.2%)	3419 (44.0%)	1086 (42.5%)	1085 (43.1%)	2171 (42.8%)
Missing	1	0	1	0	0	0
ECOG Performance Status, n (%)						
0	3000 (77.5%)	3021 (77.6%)	6021 (77.6%)	2084 (81.6%)	2027 (80.6%)	4111 (81.1%)
1	844 (21.8%)	846 (21.7%)	1690 (21.8%)	465 (18.2%)	487 (19.4%)	952 (18.8%)
2	25 (0.6%)	26 (0.7%)	51 (0.7%)	4 (0.2%)	2 (0.1%)	6 (0.1%)
Missing	1	0	1	1	1	2
T Stage, n (%)						
T0	0	1 (0.0%)	1 (0.0%)	0	2 (0.1%)	2 (0.0%)
T1	168 (4.4%)	151 (3.9%)	319 (4.1%)	88 (3.5%)	86 (3.4%)	174 (3.4%)
T2	347 (9.0%)	391 (10.2%)	738 (9.6%)	246 (9.7%)	213 (8.5%)	459 (9.1%)
T3	2617 (68.1%)	2586 (67.2%)	5203 (67.7%)	1602 (62.9%)	1595 (63.5%)	3197 (63.2%)
T4	709 (18.5%)	718 (18.7%)	1427 (18.6%)	611 (24.0%)	617 (24.6%)	1228 (24.3%)
Missing	29	46	75	7	4	11
N Stage, n (%)						
N0	3 (0.1%)	3 (0.1%)	6 (0.1%)	2 (0.1%)	1 (0.0%)	3 (0.1%)
N1	2762 (72.0%)	2792 (72.6%)	5554 (72.3%)	1821 (71.4%)	1793 (71.3%)	3614 (71.4%)
N2	1072 (27.9%)	1049 (27.3%)	2121 (27.6%)	726 (28.5%)	720 (28.6%)	1446 (28.6%)
Missing	33	49	82	5	3	8
Risk Group, n (%)						
T1-3 N1	2311 (60.3%)	2308 (60.1%)	4619 (60.2%)	1433 (56.3%)	1419 (56.5%)	2852 (56.4%)
T4 or N2	1523 (39.7%)	1531 (39.9%)	3054 (39.8%)	1111 (43.7%)	1091 (43.5%)	2202 (43.6%)
Missing	36	54	90	10	7	17
Number of Lymph Nodes Examined						
Median (Range)	19.0 (0, 132)	19.0 (1, 99)	19.0 (0, 132)	19.0 (2, 104)	19.0 (1, 122)	19.0 (1, 122)
Missing	694	711	1405	1336	1322	2658
Histological Grade, n (%)						
Grade 1/2	1624 (84.5%)	1670 (85.2%)	3294 (84.9%)	1062 (88.0%)	1043 (88.4%)	2105 (88.2%)
Grade 3/4	297 (15.5%)	290 (14.8%)	587 (15.1%)	145 (12.0%)	137 (11.6%)	282 (11.8%)
Missing	1949	1933	3882	1347	1337	2684

Supplementary Table 4. Selected Adverse Events, According to Treatment and Duration of Therapy.*

Adverse Event	FOLFOX					CAPOX				
	Number of Patients with Available Adverse Event Data	Grade 1	Grade 2 *number (percent)*	Grade 3 or 4	P Value	Number of Patients with Available Adverse Event Data	Grade 1	Grade 2 *number (percent)*	Grade 3 or 4	P Value
Any adverse event					<0.001					<0.001
3 mo	3283	1008 (30.7)	1039 (31.6)	1236 (37.6)		1416	496 (35.0)	578 (40.8)	342 (24.2)	
6 mo	3293	363 (11.0)	1056 (32.1)	1874 (56.9)		1389	203 (14.6)	674 (48.5)	512 (36.9)	
Peripheral sensory neurotoxicity†					<0.001					<0.001
3 mo	3191	2661 (83.4)	450 (14.1)	80 (2.5)		1412	1211 (85.8)	164 (11.6)	37 (2.6)	
6 mo	3255	1700 (52.2)	1036 (31.8)	519 (15.9)		1387	763 (55.0)	500 (36.0)	124 (8.9)	
Diarrhea					<0.001					0.01
3 mo	3114	2611 (83.8)	356 (11.4)	147 (4.7)		1414	1171 (82.8)	139 (9.8)	104 (7.4)	
6 mo	3163	2525 (79.8)	411 (13.0)	227 (7.2)		1388	1090 (78.5)	176 (12.7)	122 (8.8)	
Febrile neutropenia					0.33					0.04
3 mo	2966	2897 (97.7)	7 (0.2)	62 (2.1)		1415	1407 (99.4)	6 (0.4)	2 (0.1)	
6 mo	3021	2933 (97.1)	20 (0.7)	68 (2.3)		1390	1373 (98.8)	9 (0.6)	8 (0.6)	
Neutropenia					<0.001					<0.001
3 mo	1974	1310 (66.4)	264 (13.4)	400 (20.3)		1223	898 (73.4)	231 (18.9)	94 (7.7)	
6 mo	2010	1087 (54.1)	389 (19.4)	534 (26.6)		1197	733 (61.2)	321 (26.8)	143 (11.9)	
Thrombocytopenia					<0.001					<0.001
3 mo	1970	1812 (92.0)	139 (7.1)	19 (1.0)		1223	1104 (90.3)	93 (7.6)	26 (2.1)	
6 mo	2004	1703 (85.0)	264 (13.2)	37 (1.8)		1197	966 (80.7)	181 (15.1)	50 (4.2)	
Nausea					<0.001					0.02
3 mo	1973	1729 (87.6)	213 (10.8)	31 (1.6)		1224	1070 (87.4)	117 (9.6)	37 (3.0)	
6 mo	2008	1636 (81.5)	327 (16.3)	45 (2.2		1197	997 (83.3)	163 (13.6)	37 (3.1)	
Vomiting					0.29					0.91
3 mo	1970	1863 (94.6)	82 (4.2)	25 (1.3)		1224	1151 (94.0)	48 (3.9)	25 (2.0)	
6 mo	2006	1878 (93.6)	101 (5.0)	27 (1.3)		1197	1119 (93.5)	62 (5.2)	16 (1.3)	
Mucositis					<0.001					0.007
3 mo	1081	1029 (95.2)	44 (4.1)	8 (0.7)		1117	1085 (97.1)	29 (2.6)	3 (0.3)	
6 mo	1099	1005 (91.4)	76 (6.9)	18 (1.6)		1104	1050 (95.1)	44 (4.0)	10 (0.9)	
Fatigue					<0.001					<0.001
3 mo	1971	1722 (87.4)	215 (10.9)	34 (1.7)		1224	1130 (92.3)	82 (6.7)	12 (1.0)	
6 mo	2003	1594 (79.6)	327 (16.3)	82 (4.1)		1197	1034 (86.4)	129 (10.8)	34 (2.8)	
Hand–foot syndrome					0.03					<0.001
3 mo	311	307 (98.7)	4 (1.3)	0		693	654 (94.4)	34 (4.9)	5 (0.7)	
6 mo	306	294 (96.1)	11 (3.6)	1 (0.3)		688	593 (86.2)	77 (11.2)	18 (2.6)	

* Listed are the maximal grades of adverse events that were reported during the treatment period. In addition to the listed grades of adverse events, 19 patients had grade 5 events. In the SCOT trial, data regarding adverse events were collected only for the first 617 patients who were enrolled. P values are for the overall comparison of the three grade levels. All the P val- ues were calculated by means of the chi-square test for trend.

† The listed grades of peripheral sensory neurotoxicity represent the maximal levels at any time after randomization.

Supplemental Table 5: Disease-free survival by regimen and risk group

DFS = disease-free survival, HR = hazard ratio, CI = confidence interval

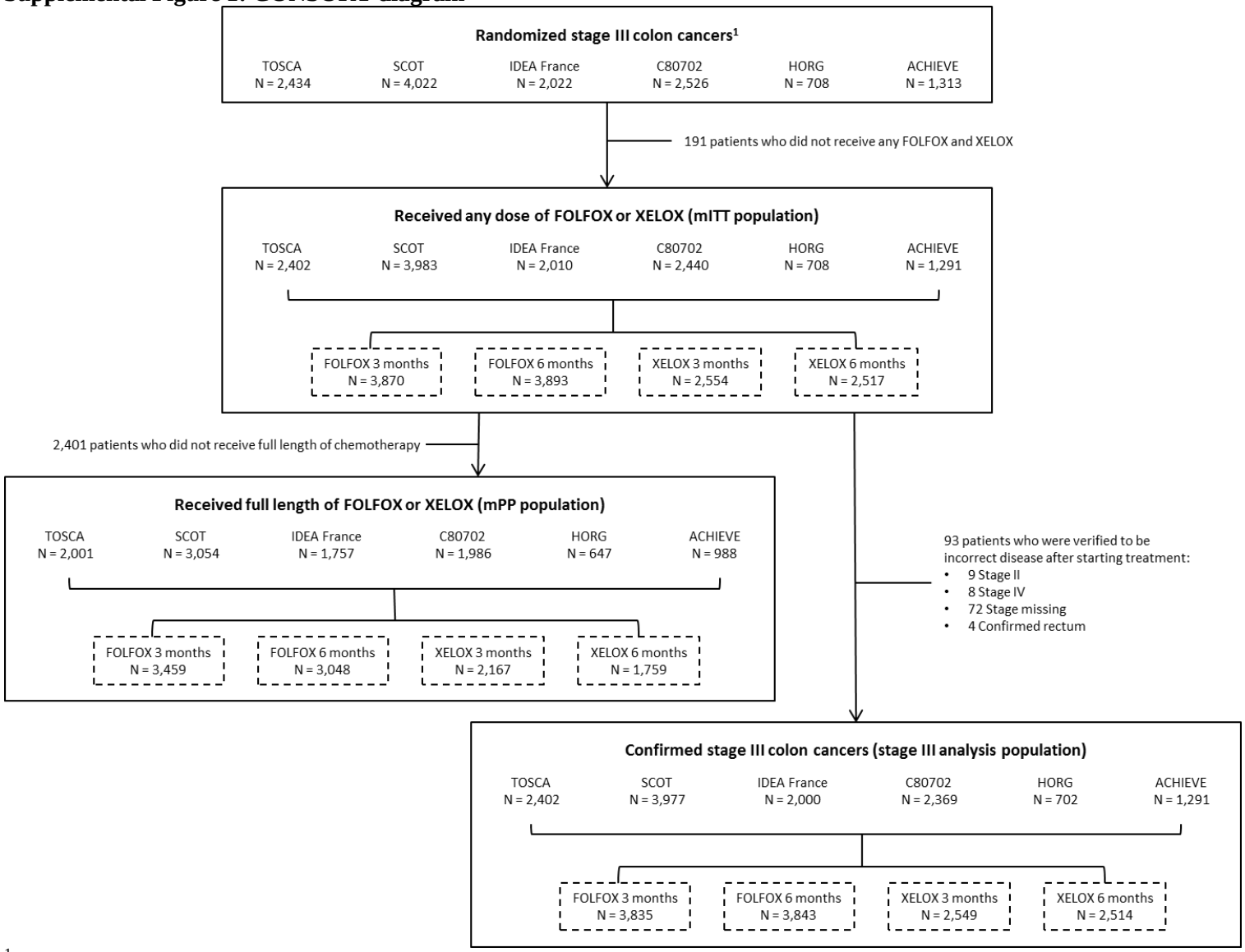
3 yr DFS rate (%) and HR by regimen and risk group		Regimen								
		CAPOX			FOLFOX			CAPOX/FOLFOX combined		
		3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)		HR (95% CI)
		3 m	6 m		3 m	6 m		3 m	6 m	
Risk group	Low-risk (T1-3 N1) ~60%	85.0 (83.1-86.9)	83.1 (81.1-85.2)	*0.85* *(0.71-1.01)*	81.9 (80.2-83.6)	83.5 (81.9-85.1)	*1.10* *(0.96-1.26)*	83.1 (81.8-84.4)	83.3 (82.1-84.6)	*1.01* *(0.90-1.12)*
	High-risk (T4 and / or N2) ~40%	64.1 (61.3-67.1)	64.0 (61.2-67.0)	*1.02* *(0.89-1.17)*	61.5 (58.9-64.1)	64.7 (62.2-67.3)	*1.20* *(1.07-1.35)*	62.7 (60.8-64.4)	64.4 (62.6-66.4)	*1.12* *(1.03-1.23)*
	Risk groups combined	75.9 (74.2-77.6)	74.8 (73.1-76.6)	*0.95* *(0.85-1.06)*	73.6 (72.2-75.1)	76.0 (74.6-77.5)	*1.16* *(1.06-1.26)*	P-value interaction test: Regimen: 0.0061 Risk group: 0.11		

Non-inferior | Not proven | Inferior

Supplemental Table 6: Disease evaluation and follow-up by study

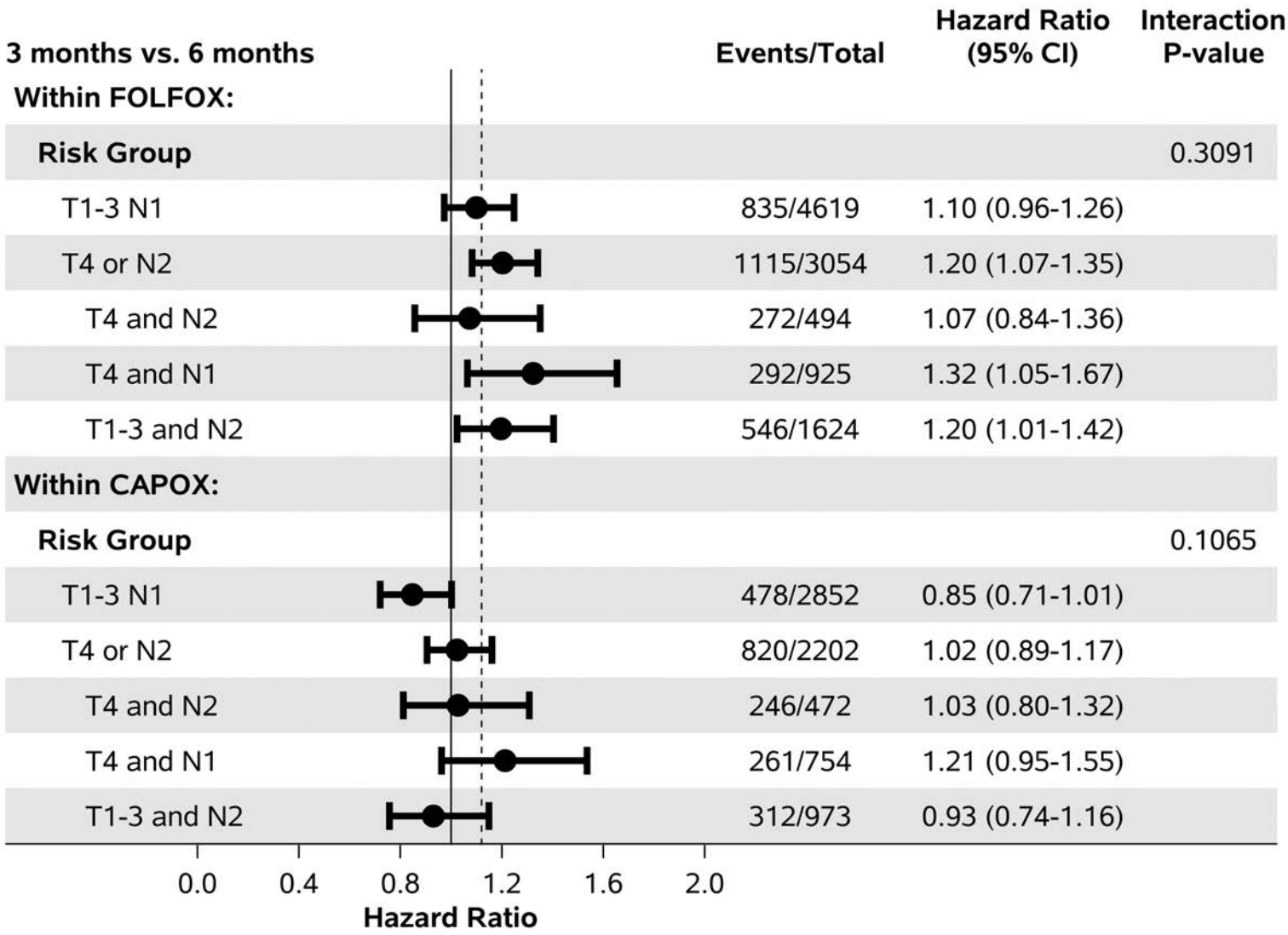
Study	3 Month arm	6 Month arm
ACHIEVE	Every 6 months up to 6 years post registration.	
C80702	First imaging within 4 months after completion of FOLFOX, then every 6 months until at least 3 years after initiation of celecoxib/placebo, then yearly for 3 years or until PD	First imaging within 6 weeks of finishing FOLFOX then same as 3 months arm.
IDEA France	Every 6 months until year 3 then yearly until year 8	At month 3 and 6. Then every 6 months until year 3; then yearly until year 8.
HORG	First assessment at month 12, then every 6 months until year 3, then every 12 months until year 8.	
SCOT	Every 6 months post-registration, up to 3 years.	
TOSCA	FOLFOX: 6 months follow-up visit, then every 6 months up to 5 years. CAPOX: 6 months follow-up visit, then every 6 months up to 3 years.	FOLFOX: 3-4 weeks end of treatment visit (~6 months) and every 6 months up to 5 years. CAPOX: 3-4 weeks end of treatment visit (~6 months) and every 6 months up to 3 years

Supplemental Figure 1: CONSORT diagram



[1]stage III colon cancer deemed at registration

Supplemental Figure 2: Comparing DFS between patients assigned to 3m vs. 6m of adjuvant therapy by subgroups



DFS, disease-free survival; CI, confidence interval

Supplemental Figure 3: Forest plots of individual trial results by regimen and risk group

Supplemental Fig 3A: Results for FOLFOX in high-risk group

FOLFOX: T4 or N2 3 months vs. 6 months	Total	Hazard Ratio (95% CI)	Sup p	NI p
ACHIEVE (p-value 0.3250)	158	1.13 (0.69-1.85)	0.6328	0.5120
SCOT	646	1.10 (0.85-1.42)	0.4767	0.4421
HORG	136	0.89 (0.52-1.52)	0.6618	0.1968
TOSCA	548	1.02 (0.77-1.36)	0.8733	0.2645
IDEA France	702	1.44 (1.14-1.82)	0.0022	0.9824
C80702	864	1.30 (1.03-1.64)	0.0278	0.8919
All Studies	3054	1.20 (1.07-1.35)	0.0021	0.8825

Supplemental Fig 3B: Results for FOLFOX in low-risk group

FOLFOX: T1-3 N1 3 months vs. 6 months	Total	Hazard Ratio (95% CI)	Sup p	NI p
ACHIEVE ḅ p-value 0.2254	164	1.22 (0.56-2.65)	0.6195	0.5828
SCOT	687	1.40 (0.95-2.07)	0.0852	0.8728
HORG	158	0.67 (0.33-1.39)	0.2766	0.0834
TOSCA	997	1.23 (0.94-1.60)	0.1259	0.7554
IDEA France	1106	1.15 (0.89-1.49)	0.2847	0.5838
C80702	1507	0.89 (0.68-1.15)	0.3767	0.0413
All Studies	4619	1.10 (0.96-1.26)	0.1697	0.3968

Supplemental Fig 3C: Results for CAPOX in high-risk group

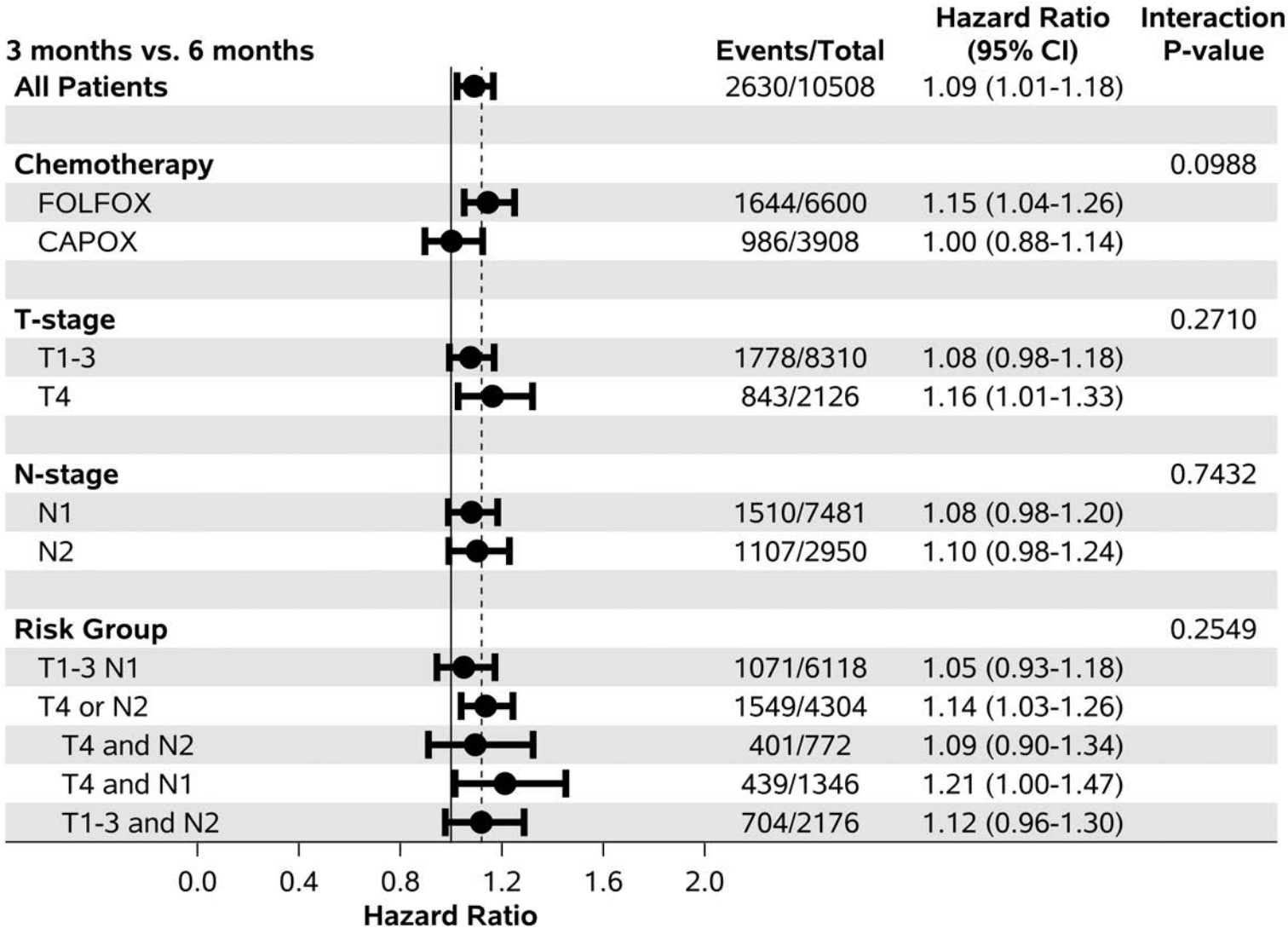
CAPOX: T4 or N2 3 months vs. 6 months	Total	Hazard Ratio (95% CI)	Sup p	NI p
ACHIEVE b p-value 0.9339	415	1.10 (0.79-1.55)	0.5664	0.4681
SCOT	1304	1.04 (0.88-1.24)	0.6396	0.2080
HORG	152	0.89 (0.52-1.53)	0.6782	0.2033
TOSCA	269	0.94 (0.63-1.40)	0.7532	0.1930
IDEA France	62	0.87 (0.40-1.88)	0.7227	0.2606
C80702				
All Studies	2202	1.02 (0.89-1.17)	0.7454	0.0974

Supplemental Fig 3D: Results for CAPOX in low-risk group

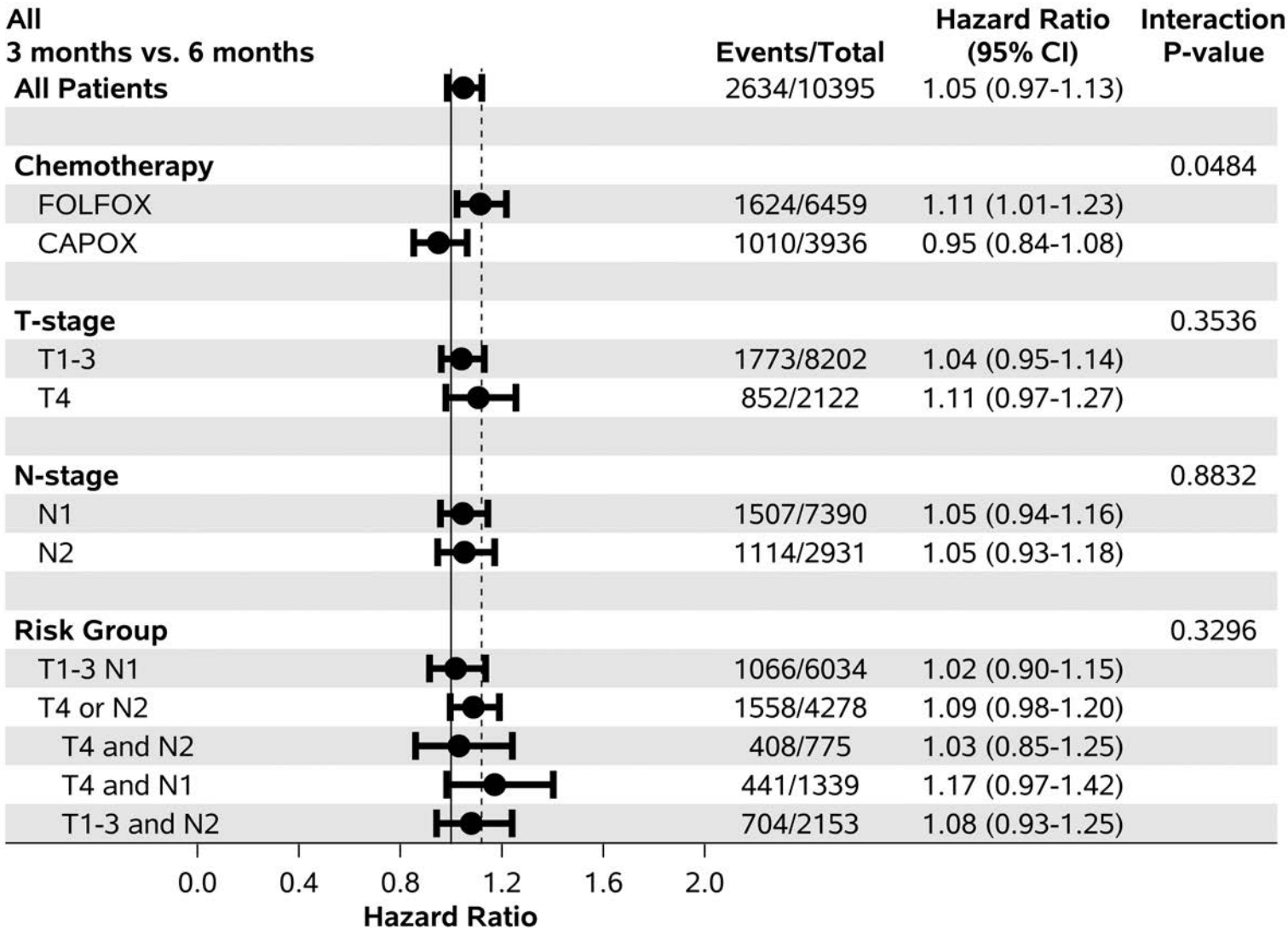
CAPOX: T1-3 N1 3 months vs. 6 months	Total	Hazard Ratio (95% CI)	Sup p	NI p
ACHIEVE b p-value 0.2846	554	0.60 (0.35-1.03)	0.0595	0.0118
SCOT	1345	0.75 (0.58-0.98)	0.0343	0.0016
HORG	258	1.31 (0.80-2.15)	0.2812	0.7351
TOSCA	556	0.92 (0.62-1.36)	0.6638	0.1600
IDEA France	139	1.10 (0.58-2.10)	0.7691	0.4793
C80702				
All Studies	2852	0.85 (0.71-1.01)	0.0701	0.0012

Supplemental Fig 4: Forest plots of results in the per-protocol population

Supplemental Fig 4A: Results comparing 3 months versus patients receiving at least 5 months of adjuvant therapy



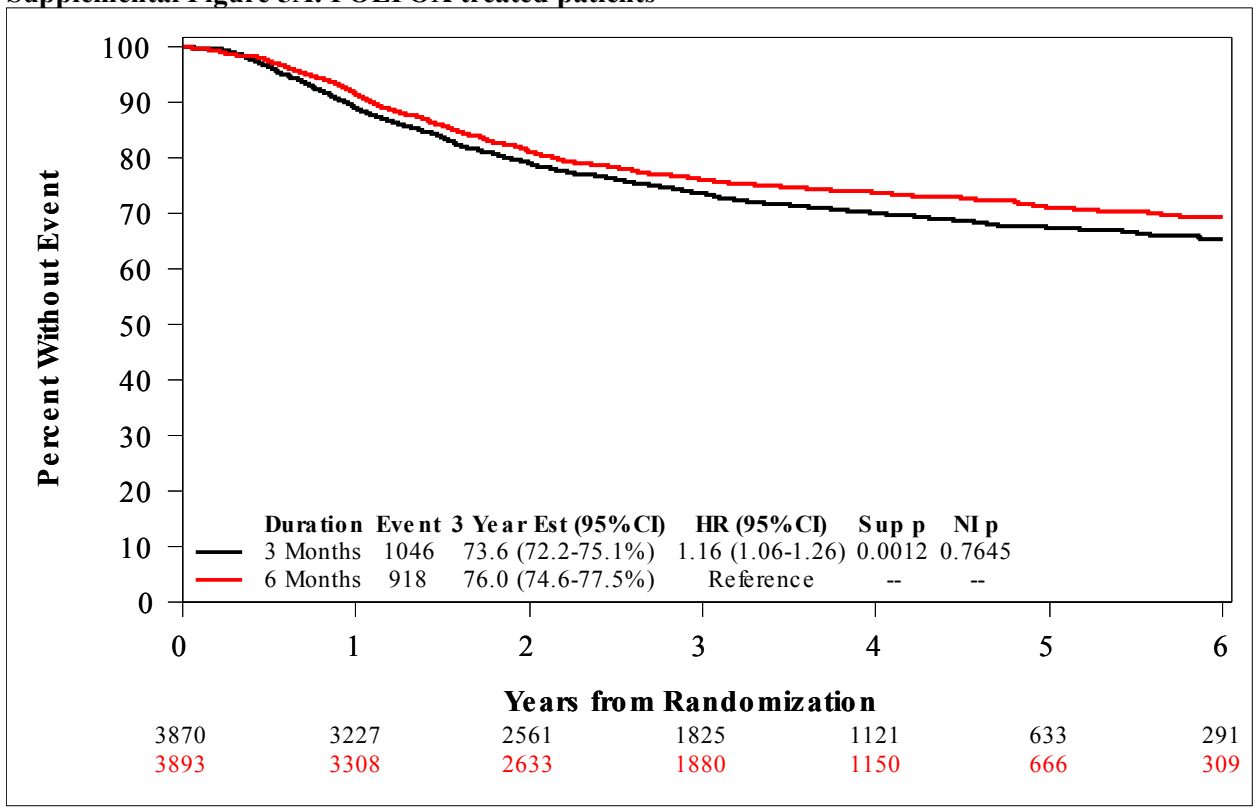
Supplemental Fig 4B: Results comparing 3 months versus patients receiving 6 months of adjuvant therapy



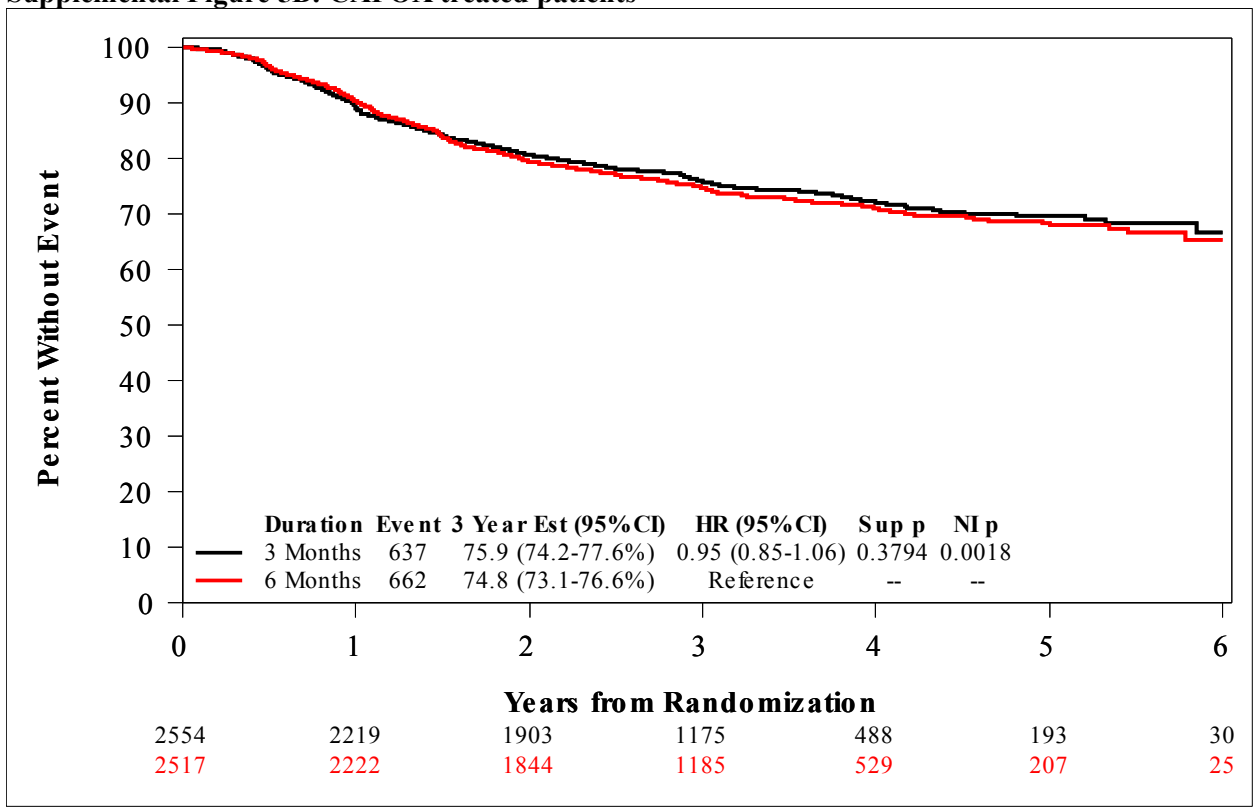
Supplemental Figure 5: Comparing DFS between patients assigned to 3m vs. 6m of adjuvant treatment (mITT) per subgroup

Footnote: DFS, disease-free survival; CI, confidence interval; HR, hazard ratio; Sup p, p-value of stratified Log-rank test for two-sided superiority testing; NI p, p-value of stratified non-inferiority testing; 3 year estimate, 3 year DFS rate derived based on Kaplan-Meier estimates; Numbers under the plot are number of patients at risk;

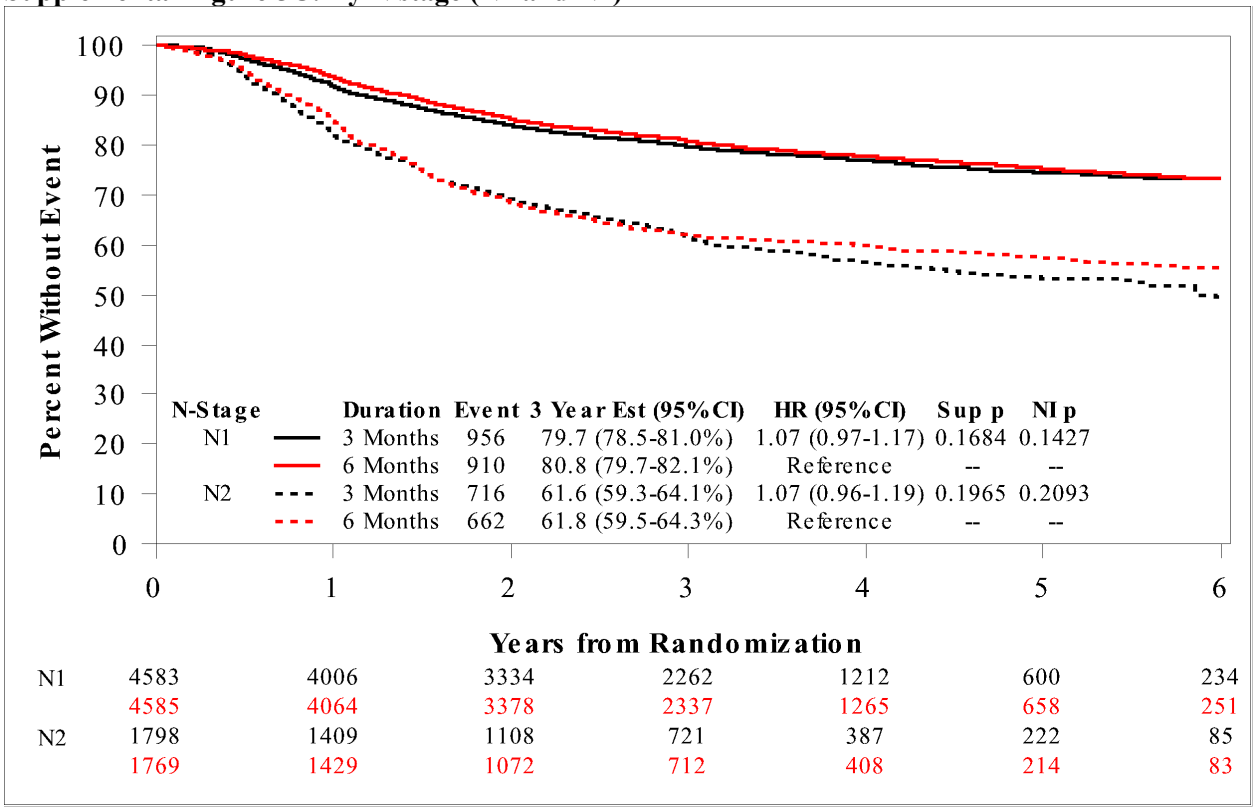
Supplemental Figure 5A: FOLFOX treated patients



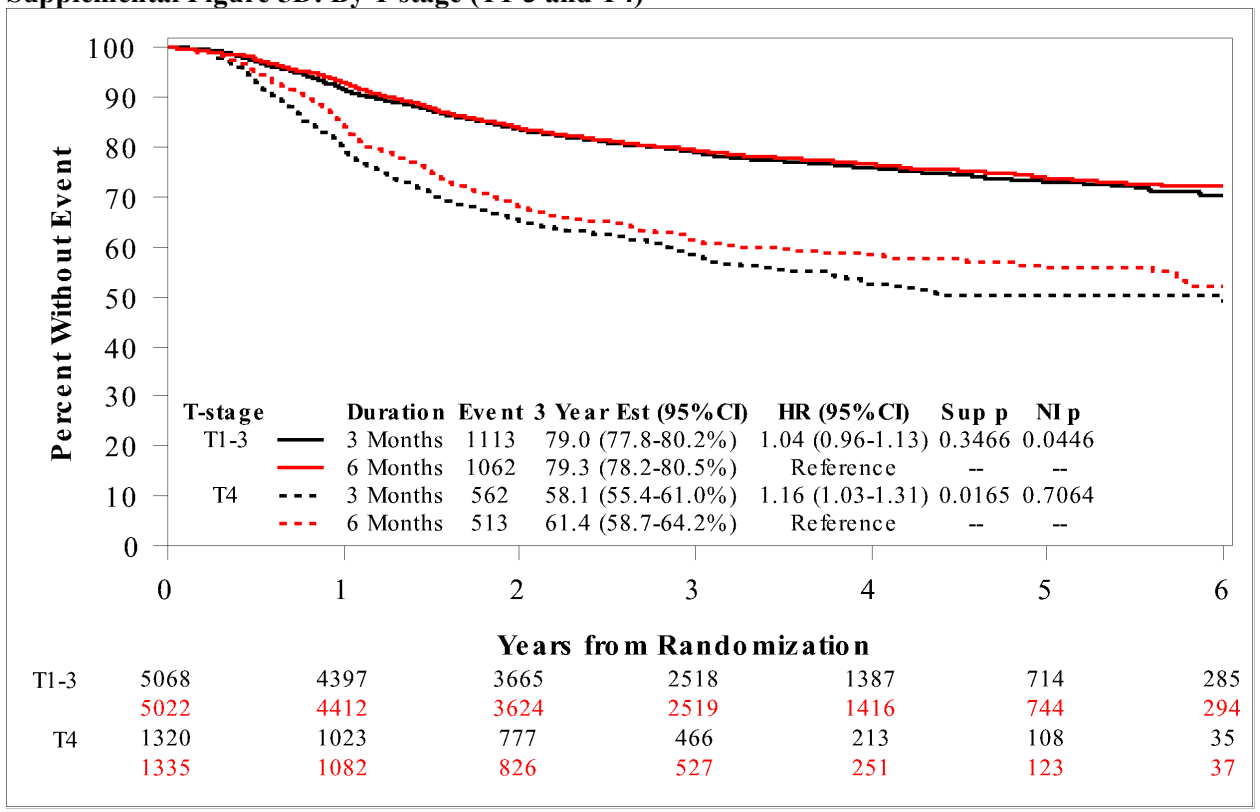
Supplemental Figure 5B: CAPOX treated patients



Supplemental Figure 5C: By N stage (N1 and N2)



Supplemental Figure 5D: By T stage (T1-3 and T4)



Supplemental Figure 5E: By risk group (T1-3 N1 and T4 and/or N2)