Supplementary Table 1. Univariate and multivariate Cox models for progression-free survival in patients with MSI metastatic colorectal cancer from sporadic and familial origin

		MSI sporadic							MSI familial						
			Univariate analysis			Multivariate analysis				Univariate analysis			Multivariate analysis		
		N (events)	HR	95%CI	P	HR	95%CI	P	N (events)	HR	95%CI	P	HR	95%CI	P
Gender	Male	19 (15)	1						41 (34)	1			1		
	Female	48 (38)	1.07	0.59-1.96	0.82				20 (11)	0.44	0.22-0.88	0.02	0.40	0.20-0.82	0.01
Age (years) †	<Median	30 (23)	1						33 (25)	1					
	≥Median	37 (30)	0.79	0.46-1.38	0.41				28 (20)	0.67	0.36-1.23	0.20			
ECOG PS	0-1	33 (25)	1						25 (17)	1					
	≥2	9 (9)	1.9	0.87-4.16	0.11				11 (8)	1.31	0.56-3.07	0.54			
Primary tumor localization	Right side	58 (46)	1						33 (22)	1					
	Left side	8 (6)	0.93	0.39-2.18	0.86				18 (14)	1.1	0.55-2.20	0.79			
Surgery of primary tumor	No	4 (4)	1						8 (8)	1			1		
	Yes	63 (49)	0.40	0.14-1.13	0.09 *				53 (37)	0.44	0.20-0.97	0.04	0.32	0.14-0.74	0.01
Synchronicity of metastases	Synchronous	39 (31)	1						36 (26)	1					
	Metachronous	28 (22)	1.36	0.78-2.36	0.27				25 (19)	0.59	0.30-1.15	0.12			
Number of metastatic sites	1	46 (34)	1			1			36 (22)	1					
	≥2	21 (19)	1.70	0.96-3.01	0.07	1.65	0.92-2.94	0.09	25 (23)	1.43	0.79-2.58	0.24			
Liver metastases	No	49 (42)	1						30 (21)	1					
	Yes	18 (11)	0.72	0.37-1.41	0.34				31 (24)	1.21	0.66-2.21	0.54			
Lung metastases	No	56 (44)	1						55 (41)	1					
	Yes	11 (9)	0.68	0.33-1.40	0.29				6 (4)	0.98	0.35-2.77	0.97			
Peritoneal metastases	No	38 (26)	1			1			32 (23)	1					
	Yes	29 (27)	1.63	0.94-2.83	0.08	1.54	0.88-2.67	0.13	29 (22)	1.21	0.65-2.22	0.55			
Lymph nodes metastases	No	41 (31)	1						43 (30)	1					
	Yes	26 (22)	1.13	0.66-1.96	0.65				18 (15)	0.8	0.42-1.52	0.50			
Tumor differentiation	Well /moderate	30 (23)	1						34 (26)	1					
	Poor	27 (25)	1.34	0.76-2.36	0.32				20 (13)	0.76	0.39-1.48	0.42			
BRAF status	Wild-type	17 (13)	1						53 (40)	1					
	Mutated	50 (40)	0.88	0.47-1.65	0.69				4 (2)	0.73	0.17-3.06	0.67			
KRAS exon 2 status	Wild-type	62 (49)	1						36 (26)	1					
	Mutated	5 (4)	2.88	0.99-8.41	0.05 *				19 (14)	1.04	0.54-2.02	0.91			
Chemotherapy regimen	Folfox-based	38 (29)	1						32 (24)	1					
	Folfiri-based	14 (11)	0.73	0.35-1.55	0.41				19 (14)	0.75	0.38-1.48	0.41			
Anti-EGFR-based chemotherapy	No	52 (43)	1			1			44 (33)	1			1		
	Yes	15 (10)	0.80	0.39-1.60	0.52	0.75	0.37-1.51	0.42	17 (12)	0.47	0.23-0.94	0.03	0.49	0.24-0.98	0.04

Anti-EGFR-based chemotherapy and variables with P value <0.10 in univariate analysis were included in multivariate model (except variables including less than 5 patients in one of their categories, i.e. surgery of primary tumor and KRAS exon 2 status in MSI sporadic *)

† The cut-off for age was based on the median age in sporadic (70 years) and familial (50 years) MSI cases

Abbreviations: MSI, microsatellite instability; EGFR, epidermal growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, Hazard Ratio; 95%CI, confidence interval

Supplementary Table 2. Efficacy in progression-free survival of adding anti-EGFR to first-line chemotherapy based on propensity score with logistic regression in patients with MSI metastatic colorectal cancer from sporadic and familial origin

		MSI sporadic								MSI familial							
		Univariate analysis †				Multivariate analysis †				Univariate analysis †				Multivariate analysis †			
		N (anti-EGFR therapy)	OR	95%CI	P	N (anti-EGFR therapy)	OR	95%CI	P	N (anti-EGFR therapy)	OR	95%CI	P	N (anti-EGFR therapy)	OR	95%CI	P
Gender	Male	19 (6)	1							41 (11)	1						
	Female	48 (9)	0.50	0.15-1.68	0.26					20 (6)	1.17	0.36-3.80	0.80				
Age (years)	Continuous	67 (15)	0.98	0.93-1.03	0.40					61 (17)	1.04	0.99-1.09	0.12				
ECOG PS	0-1	33 (6)	1							25 (8)	1						
	≥2	9 (2)	1.29	0.21-7.80	0.79					11 (3)	0.80	0.17-3.83	0.78				
Primary tumor localization	Right side	58 (14)	1							33 (12)	1						
	Left side	8 (1)	0.45	0.05-3.97	0.47					18 (4)	0.50	0.13-1.87	0.30				
Surgery of primary tumor	No	4 (3)	1							8 (2)	1						
	Yes	63 (12)	0.08	0.01-0.82	0.03*					53 (15)	1.18	0.22-6.54	0.85				
Synchronicity of met.	Synchronous	39 (8)	1							36 (5)	1			26 (4)	1		
	Metachronous	28 (7)	1.29	0.41-4.10	0.66					25 (12)	5.72	1.68-19.54	0.01	25 (12)	2.35	0.50-11.15	0.28
Number of met. sites	1	46 (10)	1							36 (11)	1						
	≥2	21 (5)	1.13	0.33-3.83	0.85					25 (6)	0.72	0.23-2.29	0.57				
Liver met.	No	49 (11)	1							30 (11)	1						
	Yes	18 (4)	0.99	0.27-3.62	0.98					31 (6)	0.42	0.13-1.32	0.14				
Lung met.	No	56 (13)	1							55 (15)	1						
	Yes	11 (2)	0.74	0.14-3.84	0.71					6 (2)	1.33	0.22-8.05	0.75				
Peritoneal met.	No	38 (9)	1							32 (9)	1						
	Yes	29 (6)	0.84	0.26-2.71	0.77					29 (8)	0.97	0.32-2.98	0.96				
Lymph nodes met.	No	41 (8)	1							43 (9)	1			36 (9)	1		
	Yes	26 (7)	1.52	0.48-4.85	0.48					18 (8)	3.02	0.92-9.88	0.07	15 (7)	1.94	0.4-8.06	0.38
Tumor differentiation	Well /moderate	30 (3)	1			23 (3)	1			34 (7)	1						
	Poor	27 (8)	3.79	0.89-16.17	0.07	22 (8)	4.27	0.82-22.19	0.08	20 (8)	2.57	0.76-8.72	0.13				
BRAF status	Wild-type	17 (4)	1							53 (15)	1						
	Mutated	50 (11)	0.92	0.25-3.38	0.90					4 (2)	2.53	0.33-19.66	0.37				
Chemotherapy	Folfox-based	38 (31)	1			34 (5)	1			32 (4)	1			36 (9)	1		
	Folfiri-based	14 (6)	5.91	1.54-22.53	0.01	11 (6)	7.64	1.50-39.03	0.01	19 (12)	12	2.95-48.76	<.001	15 (7)	1.94	0.4-8.06	0.38

		IPTW Cox analysis ††				IPTW Cox analysis ††			
		N (events)	HR	95%CI	P	N (events)	HR	95%CI	P
Anti-EGFR-based chemo.	No	34 (28)	1			35 (26)	1		
	Yes	11 (9)	0.80	0.50-1.26	0.34	16 (12)	0.63	0.41-0.97	0.04

In order to limit potential bias due to confounding parameters unbalanced between treatment arms in sporadic and familial MSI groups, the inverse probability of treatment weighting method (IPTW) was applied in the Cox regression model using the propensity score.

† The probability to receive anti-EGFR therapy was estimated using logistic regression analysis for each clinical and pathological characteristics and odds ratio (OR) with 95% confidence interval (CI) were provided. Except variables with less than 5 patients in one of their category (i.e. surgery of primary tumor for MSI sporadic*), those with P value <0.10 in univariate analysis were included in the multivariate logistic regression model (i.e. tumor differentiation and chemotherapy regimen for MSI sporadic; i.e. synchronicity of metastases, lymph nodes metastases and chemotherapy regimen for MSI familial). †† The propensity score, derived from the multivariate logistic model, was used in the inverse probability of treatment weighting methodology (IPTW) applied in the univariate cox regression to evaluate the efficacy of adding anti-EGFR agents in terms of progression-free survival.

Abbreviations: MSI, microsatellite instability; Met, Metastases; Chemo, Chemotherapy; EGFR, epidermal growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, Hazard Ratio; OR, Odds Ratio; 95%CI, confidence interval