



	<i>CT+TT</i>	1256	310	1.04	0.85-1.27	0.71	831	211	1.02	0.80-1.31	0.86	412	94	1.02	0.72-1.46	0.90	1256	462	1.14	0.96-1.36	0.12	831	300	1.04	0.85-1.29	0.70	412	156	1.35	1.00-1.81	<b>0.05</b>
	<i>CC+CT</i>	1415	353	Ref			920	241	Ref			483	109	Ref			1415	512	Ref			920	334	Ref			483	174	Ref		
	<i>TT</i>	384	91	1.01	0.80-1.27	0.96	252	59	0.93	0.70-1.24	0.63	126	30	1.16	0.78-1.74	0.47	384	133	0.99	0.82-1.20	0.93	252	88	1.00	0.79-1.26	0.97	126	42	0.96	0.69-1.35	0.83
<b>Austria</b>																															
<b>rs12450550</b>	<i>EME1</i>	<i>TT</i>	564	119	Ref		348	75	Ref			206	42	Ref			564	164	Ref			348	99	Ref			206	63	Ref		
	<i>TC</i>	325	66	0.95	0.70-1.28	0.72	196	43	0.99	0.68-1.44	0.97	123	23	0.92	0.55-1.53	0.75	325	86	0.88	0.68-1.14	0.34	196	54	0.92	0.66-1.28	0.61	123	32	0.86	0.56-1.31	0.47
	<i>CC</i>	61	6	0.43	0.19-0.97	<b>0.04</b>	38	3	0.32	0.10-1.02	<b>0.05</b>	20	3	0.76	0.23-2.44	0.64	61	9	0.47	0.24-0.91	<b>0.03</b>	38	6	0.49	0.22-1.12	0.09	20	3	0.49	0.15-1.56	0.23
	<i>TC+CC</i>	386	72	0.86	0.64-1.15	0.31	234	46	0.87	0.61-1.26	0.47	143	26	0.90	0.55-1.47	0.67	386	95	0.81	0.63-1.05	0.10	234	60	0.85	0.61-1.16	0.30	143	35	0.81	0.53-1.22	0.30
	<i>TT+TC</i>	889	185	Ref			544	118	Ref			329	65	Ref			889	250	Ref			544	153	Ref			329	95	Ref		
	<i>CC</i>	61	6	0.44	0.19-0.99	<b>0.05</b>	38	3	0.32	0.10-1.02	<b>0.05</b>	20	3	0.78	0.24-2.47	0.67	61	9	0.49	0.25-0.95	<b>0.03</b>	38	6	0.51	0.22-1.14	0.10	20	3	0.52	0.17-1.64	0.26
<b>rs2283432</b>	<i>FANCI</i>	<i>CC</i>	333	74	Ref		211	48	Ref			118	26	Ref			333	106	Ref			211	66	Ref			118	40	Ref		
	<i>CG</i>	462	87	0.83	0.61-1.13	0.23	284	57	0.86	0.59-1.26	0.44	165	28	0.75	0.44-1.29	0.30	462	115	0.74	0.57-0.96	<b>0.02*</b>	284	73	0.78	0.56-1.09	0.14	165	40	0.66	0.43-1.03	0.07
	<i>GG</i>	155	30	0.86	0.57-1.32	0.50	87	16	0.81	0.46-1.42	0.45	66	14	0.96	0.50-1.84	0.90	155	38	0.75	0.51-1.08	0.12	87	20	0.71	0.43-1.17	0.18	66	18	0.78	0.45-1.37	0.39
	<i>CG+GG</i>	617	117	0.84	0.63-1.12	0.23	371	73	0.85	0.59-1.22	0.37	231	42	0.81	0.50-1.32	0.40	617	153	0.74	0.58-0.95	<b>0.02</b>	371	93	0.76	0.56-1.05	0.09	231	58	0.70	0.47-1.04	0.08
	<i>CC+CG</i>	795	161	Ref			495	105	Ref			283	54	Ref			795	221	Ref			495	139	Ref			283	80	Ref		
	<i>GG</i>	155	30	0.96	0.65-1.42	0.85	87	16	0.88	0.52-1.49	0.63	66	14	1.13	0.63-2.03	0.69	155	38	0.88	0.63-1.25	0.48	87	20	0.82	0.51-1.31	0.41	66	18	0.98	0.59-1.63	0.93
<b>rs3087386</b>	<i>REV1</i>	<i>CC</i>	301	50	Ref		191	30	Ref			102	20	Ref			301	71	Ref			191	42	Ref			102	29	Ref		
	<i>CT</i>	481	106	1.38	0.99-1.93	0.06	298	67	1.55	1.01-2.39	<b>0.05</b>	175	38	1.06	0.61-1.81	0.85	481	139	1.28	0.97-1.71	0.09	298	85	1.40	0.97-2.03	0.07	175	53	1.04	0.66-1.64	0.86
	<i>TT</i>	168	35	1.31	0.85-2.02	0.22	93	24	1.81	1.06-3.10	<b>0.03</b>	72	10	0.67	0.32-1.44	0.31	168	49	1.30	0.90-1.87	0.16	93	32	1.73	1.09-2.74	<b>0.02</b>	72	16	0.74	0.40-1.36	0.33
	<i>CT+TT</i>	649	141	1.36	0.99-1.88	0.06	391	91	1.61	1.07-2.43	<b>0.02</b>	247	48	0.94	0.56-1.59	0.83	649	188	1.29	0.98-1.69	0.07	391	117	1.48	1.04-2.10	<b>0.03*</b>	247	69	0.95	0.62-1.47	0.82
	<i>CC+CT</i>	782	156	Ref			489	97	Ref			277	58	Ref			782	210	Ref			489	127	Ref			277	82	Ref		
	<i>TT</i>	168	35	1.07	0.74-1.54	0.73	93	24	1.37	0.87-2.13	0.17	72	10	0.65	0.33-1.27	0.21	168	49	1.11	0.81-1.51	0.52	93	32	1.40	0.95-2.06	0.09	72	16	0.72	0.42-1.24	0.24
<b>rs3204953</b>	<i>REV3L</i>	<i>AA</i>	699	152	Ref		424	96	Ref			260	55	Ref			699	205	Ref			424	128	Ref			260	76	Ref		
	<i>AG</i>	226	33	0.70	0.48-1.02	0.06	145	22	0.68	0.43-1.08	0.10	77	10	0.66	0.34-1.30	0.23	226	46	0.70	0.51-0.97	<b>0.03*</b>	145	28	0.62	0.41-0.94	<b>0.02</b>	77	17	0.81	0.48-1.37	0.43
	<i>GG</i>	25	6	1.16	0.51-2.63	0.72	13	3	1.15	0.36-3.61	0.82	12	3	1.17	0.37-3.73	0.79	25	8	1.18	0.58-2.39	0.65	13	3	0.81	0.26-2.54	0.72	12	5	1.59	0.65-3.94	0.31
	<i>AG+GG</i>	251	39	0.75	0.52-1.06	0.10	158	25	0.72	0.46-1.11	0.14	89	13	0.74	0.40-1.35	0.32	251	54	0.75	0.55-1.01	0.06	158	31	0.64	0.43-0.94	<b>0.02*</b>	89	22	0.91	0.57-1.47	0.70
	<i>AA+AG</i>	925	185	Ref			569	118	Ref			337	65	Ref			925	251	Ref			569	156	Ref			337	93	Ref		
	<i>GG</i>	25	6	1.25	0.56-2.83	0.59	13	3	1.25	0.40-3.94	0.70	12	3	1.26	0.40-4.01	0.70	25	8	1.27	0.63-2.57	0.50	13	3	0.90	0.29-2.82	0.85	12	5	1.67	0.68-4.10	0.27

CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval.

Significant results in bold. Results that passed the Benjamini-Hochberg FDR test for multiple comparisons are marked with an asterisk.

<sup>a</sup> Numbers may not add up to 100% of available subjects because of genotyping failure. All samples that did not give a reliable result in the first round of genotyping were resubmitted to up to two additional rounds of genotyping. Data points that were still not filled after this procedure had been left blank.



**Supplementary Table S3: SNPs associated with OS and EFS of patients receiving 5-FU-based chemotherapy without oxaliplatin in the pooled population and in groups stratified for tumor sites (Cox regression for adjusted estimates).**

Gene SNP	Genotype	Overall survival															Event free survival														
		All CRC patients					Colon cancer patients					Rectal cancer patients					All CRC patients					Colon cancer patients					Rectal cancer patients				
		N <sup>a</sup>	Events	HR	95% CI	P-Value	N <sup>a</sup>	Events	HR	95% CI	P-Value	N <sup>a</sup>	Events	HR	95% CI	P-Value	N <sup>a</sup>	Events	HR	95% CI	P-Value	N <sup>a</sup>	Events	HR	95% CI	P-Value	N <sup>a</sup>	Events	HR	95% CI	P-Value
<b>Czech Republic</b>																															
<b>FAAP24</b> rs3816032	TT	342	60	Ref			220	39	Ref			120	20	Ref			342	110	Ref			220	70	Ref			120	38	Ref		
	TC	126	27	1.21	0.77-1.90	0.42	93	19	1.10	0.64-1.91	0.73	33	8	1.48	0.65-3.36	0.35	126	37	0.89	0.62-1.30	0.55	93	25	0.79	0.50-1.25	0.32	33	12	1.18	0.61-2.25	0.63
	CC	12	5	2.14	0.86-5.35	0.10	10	4	1.70	0.61-4.77	0.31	2	1	11.07	1.35-90.62	<b>0.03</b>	12	6	1.27	0.56-2.90	0.56	10	4	0.85	0.31-2.34	0.76	2	2	7.43	1.73-32.02	<b>0.007*</b>
	TC+CC	138	32	1.29	0.84-1.98	0.24	103	23	1.17	0.70-1.97	0.54	35	9	1.63	0.74-3.58	0.23	138	43	0.93	0.66-1.33	0.69	103	29	0.80	0.52-1.24	0.32	35	14	1.34	0.72-2.47	0.36
	TT+TC	468	87	Ref			313	58	Ref			153	28	Ref			468	147	Ref			313	95	Ref			153	50	Ref		
CC	12	5	1.97	0.80-4.85	0.14	10	4	1.61	0.58-4.45	0.36	2	1	6.43	0.84-49.18	0.07	12	6	1.32	0.58-2.99	0.50	10	4	0.94	0.34-2.55	0.90	2	2	7.27	1.72-30.69	<b>0.007*</b>	
<b>RAD51D</b> rs4796033	CC	342	66	Ref			225	45	Ref			116	21	Ref			342	111	Ref			225	70	Ref			116	40	Ref		
	CT	129	24	1.04	0.65-1.66	0.88	91	17	1.07	0.61-1.87	0.81	37	6	0.82	0.33-2.03	0.66	129	35	0.85	0.58-1.24	0.40	91	25	0.98	0.62-1.55	0.93	37	9	0.59	0.29-1.21	0.15
	TT	18	3	0.79	0.25-2.53	0.70	13	1	0.33	0.05-2.36	0.27	5	2	2.66	0.62-11.38	0.19	18	9	1.49	0.75-2.93	0.25	13	5	1.02	0.41-2.52	0.97	5	4	3.98	1.40-11.33	<b>0.01*</b>
	CT+TT	147	27	1.00	0.64-1.57	0.99	104	18	0.95	0.55-1.64	0.85	42	8	0.99	0.44-2.25	0.99	147	44	0.93	0.66-1.32	0.68	104	30	0.98	0.64-1.51	0.94	42	13	0.80	0.43-1.49	0.48
	CC+CT	471	90	Ref			316	62	Ref			153	27	Ref			471	146	Ref			316	95	Ref			153	49	Ref		
TT	18	3	0.78	0.25-2.47	0.67	13	1	0.32	0.04-2.28	0.25	5	2	2.74	0.65-11.55	0.17	18	9	1.54	0.78-3.01	0.21	13	5	1.01	0.41-2.49	0.98	5	4	4.53	1.61-12.78	<b>0.004*</b>	
<b>REVI</b> rs3087399	AA	334	65	Ref			227	43	Ref			105	21	Ref			334	111	Ref			227	70	Ref			105	39	Ref		
	AG	142	27	1.02	0.65-1.59	0.95	95	20	1.12	0.66-1.90	0.68	47	7	0.84	0.36-1.97	0.68	142	42	0.89	0.62-1.27	0.52	95	29	0.96	0.62-1.48	0.86	47	13	0.80	0.43-1.49	0.48
	GG	6	2	2.16	0.53-8.82	0.28	3	1	2.44	0.34-17.77	0.38	3	1	2.14	0.29-16.00	0.46	6	3	1.76	0.56-5.55	0.33	3	2	4.10	1.00-16.91	<b>0.05</b>	3	1	0.87	0.12-6.34	0.89
	AG+GG	148	29	1.06	0.68-1.63	0.81	98	21	1.15	0.68-1.94	0.60	50	8	0.91	0.40-2.04	0.81	148	45	0.92	0.65-1.30	0.64	98	31	1.01	0.66-1.54	0.96	50	14	0.80	0.43-1.47	0.47
	AA+AG	476	92	Ref			322	63	Ref			152	28	Ref			476	153	Ref			322	99	Ref			152	52	Ref		
GG	6	2	2.16	0.53-8.79	0.28	3	1	2.44	0.34-17.58	0.38	3	1	2.21	0.30-16.31	0.44	6	3	1.83	0.58-5.74	0.30	3	2	4.00	0.98-16.33	<b>0.05</b>	3	1	0.93	0.13-6.70	0.94	
<b>Austria</b>																															
<b>POLN</b> rs9328764	AA	3	1	Ref			1	1	Ref			2	0	Ref			3	1	Ref			1	1	Ref			2	0	Ref		
	AG	76	8	0.36	0.05-2.89	0.34	35	4	0.14	0.02-1.24	0.08	40	4	NA			76	17	0.61	0.08-4.58	0.63	35	7	0.03	0.002-0.52	<b>0.02</b>	40	10	NA		
	GG	168	27	0.58	0.08-4.23	0.59	94	14	0.18	0.02-1.36	0.10	70	13	NA			168	37	0.61	0.08-4.48	0.63	94	19	0.08	0.01-0.64	<b>0.02</b>	70	18	NA		
	AG+GG	244	35	0.51	0.07-3.69	0.50	129	18	0.17	0.02-1.25	0.08	110	17	NA			244	54	0.61	0.09-4.42	0.63	129	26	0.06	0.01-0.52	<b>0.01</b>	110	28	NA		
	AA+AG	79	9	Ref			36	5	Ref			42	4	Ref			79	18	Ref			36	8	Ref			42	10	Ref		
GG	168	27	1.46	0.69-3.11	0.32	94	14	1.14	0.41-3.17	0.80	70	13	1.95	0.64-5.99	0.24	168	37	0.95	0.54-1.67	0.86	94	19	0.90	0.39-2.05	0.80	70	18	1.05	0.49-2.28	0.90	

CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval.

Significant results in bold. Results that passed the Benjamini-Hochberg FDR test for multiple comparisons are marked with an asterisk.

<sup>a</sup>Numbers may not add up to 100% of available subjects because of genotyping failure. All samples that did not give a reliable result in the first round of genotyping were resubmitted to up to two additional rounds of genotyping. Data points that were still not filled after this procedure had been left blank.



	<i>CT+TT</i>	74	21	0.95	0.57-1.58	0.85	51	14	0.99	7.20 0.52- 1.86	0.97	22	7	0.95	0.40-2.24	0.91	74	33	1.02	3.99 0.68- 1.53	0.94	51	21	0.99	3.84 0.59- 1.65	0.96	22	12	1.13	0.58-2.21	0.73
	<i>CC+CT</i>	246	70	Ref			158	43	Ref			86	27	Ref			246	107	Ref			158	67	Ref			86	40	Ref		
	<i>TT</i>	6	2	1.55	0.38-6.30	0.54	5	1	0.98	0.14- 7.15	0.99	1	1	4.28	0.57- 32.30	0.16	6	2	0.96	0.24- 3.90	0.96	5	1	0.53	0.07- 3.80	0.53	1	1	10.86	1.34- 88.28	<b>0.03</b>
<b>REV3L</b>	<i>GG</i>	186	57	Ref			120	35	Ref			64	22	Ref			186	88	Ref			120	55	Ref			64	33	Ref		
<b>rs3204953</b>	<i>GA</i>	62	13	0.71	0.39-1.30	0.27	41	7	0.60	0.27- 1.36	0.22	21	6	0.87	0.35-2.14	0.76	62	19	0.62	0.38- 1.02	0.06	41	11	0.55	0.29- 1.05	0.07	21	8	0.73	0.34-1.59	0.43
	<i>AA</i>	4	2	2.30	0.56-9.44	0.25	2	2	53.33	8.70- 327.02	<b>&lt;.0001*</b>	2	0	NA			4	2	1.19	0.29- 4.81	0.81	2	2	6.24	1.45- 26.83	<b>0.01*</b>	2	0	NA		
	<i>GA+AA</i>	66	15	0.78	0.44-1.39	0.40	43	9	0.77	0.37- 1.61	0.49	23	6	0.76	0.31-1.88	0.56	66	21	0.65	0.40- 1.04	0.07	43	13	0.64	0.35- 1.17	0.15	23	8	0.64	0.30-1.39	0.26
	<i>GG+GA</i>	248	70	Ref			161	42	Ref			85	28	Ref			248	107	Ref			161	66	Ref			85	41	Ref		
	<i>AA</i>	4	2	2.51	0.62- 10.25	0.20	2	2	70.36	11.47- 431.53	<b>&lt;.0001*</b>	2	0	NA			4	2	1.32	0.33- 5.34	0.70	2	2	7.45	1.75- 31.81	<b>0.007*</b>	2	0	NA		

CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval; NA, not applicable.

Significant results in bold. Results that passed the Benjamini-Hochberg FDR test for multiple comparisons are marked with an asterisk.

<sup>a</sup> Numbers may not add up to 100% of available subjects because of genotyping failure. All samples that did not give a reliable result in the first round of genotyping were resubmitted to up to two additional rounds of genotyping. Data points that were still not filled after this procedure had been left blank.

#### *Add 2.4. Survival and Therapy*

##### **Group 1 (Supplementary Table S2)**

**Czech sample set.** In the group of CRC patients receiving no treatment, carriers of the CG genotype in *MUS81* rs545500 were associated with increased EFS (CG vs. CC; HR 0.60; 95% CI 0.41-0.90; P = 0.01 and CG+GG vs. CC; HR 0.68; 95% CI 0.47-0.98; P = 0.04). The association remained significant by tumor sub-site. Although the decreased EFS (and OS as well) was observed in the recessive model for rectal cancer patients (GG vs. CC+CG OS: HR 2.38; 95% CI 1.43-3.96; P = 0.0009 and EFS: HR 2.06; 95% CI 1.36-3.11; P = 0.0007).

In rectal cancer patients, rs3218649 and rs1381057 in the *POLQ* gene were significantly associated with OS in the codominant and dominant models (rs3218649 GC+CC vs. GG; HR 2.09; 95% CI 1.20-3.64; P = 0.009; rs1381057 CT+TT vs. CC; HR 1.88; 95% CI 1.13-3.14; P = 0.02). Additionally, carriers of the variant GG genotype in *REV1* rs3087399 showed decreased EFS when compared with the most frequent AA genotype (HR 4.89; 95% CI 1.74-13.74; P = 0.003) or with A-allele carriers (HR 5.45; 95% CI 1.97-15.14; P = 0.001). However, in this case given the low numbers of patients with the variant genotype, the result should be considered with caution.

**Austrian sample set.** In colon cancer patients, carriers of the variant GG genotype in *POLE* rs5744934 were associated with decreased OS and EFS in both codominant and recessive models (GG vs. AA+AG OS: HR 5.40; 95% CI 1.31-22.29; P = 0.02 and EFS: HR 4.67; 95% CI 1.14-19.17; P = 0.03).

##### **Group 2 (Supplementary Table S3)**

**Czech sample set.** In patients undergoing 5-FU-based chemotherapy without oxaliplatin, there was no significant association with survival outcomes by genotype for all CRC patients. For colon cancer, only the homozygous variant genotype in *REV1* rs3087399 was marginally significantly associated with decreased OS (GG vs. AA; HR 4.10; 95% CI 1.00-16.91; P = 0.05). Two SNPs were associated with survival in rectal cancer patients. The TT variant genotype in *RAD51D* rs4796033 was associated with decreased OS in the codominant and recessive models (TT vs. CC; HR 3.98; 95% CI 1.40-11.33; P = 0.01; TT vs. CC+CT; HR 4.53; 95% CI 1.61-12.78; P = 0.004) while the variant CC genotype in *FAAP24* rs38116032 was associated with both OS and EFS in different genetic models (although with wide confidence intervals).

**Austrian sample set.** In colon cancer patients, the variant G-allele carriers in *POLN* rs9328764 were associated with increased EFS in codominant and dominant models (GG vs. AA; HR 0.08; 95% CI 0.01-0.64; P = 0.02 and AG+GG vs. AA; HR 0.06; 95% CI 0.01-0.52; P = 0.01).

##### **Group 3 (Supplementary Table S4)**

**Czech sample set.** Considering all CRC patients receiving 5-FU in combination with oxaliplatin, carriers of heterozygous genotypes in *FAAP24* rs3816032 and *POLQ* rs3218651 were associated with increased OS. In both cases the significance was reached in the codominant and dominant models, however, due to the low frequency of the homozygous variant genotypes in our patient group it was not possible to observe the same effect in the codominant model. Additionally, carriers of the variant GG genotype in *POLE* rs5744934 showed decreased EFS (GG vs. AA; HR 3.07; 95% CI 1.12-8.42; P = 0.03 and GG vs. AA+AG; HR 3.24; 95% CI 1.19-8.82; P = 0.02). The association of all three SNPs remained significant after stratification according to tumor localization. In colon cancer patients, two more SNPs were associated with decreased EFS (CC genotype in *FAAP24* rs3816032: CC vs. TT+TC; HR 4.01; 95% CI 0.98-16.31; P = 0.05 and TT genotype in *POLQ* rs1381057: TT vs. CC; HR 1.98; 95% CI 1.11-3.54; P = 0.02 and TT vs. CC+CT; HR 2.06; 95% CI 1.18-3.59; P = 0.01).

In rectal cancer patients two notable associations were detected: Carriers of the variant AA genotype in *REV3L* rs3204953 showed worse OS (AA vs. GG+GA; HR 35.51; 95% CI 3.22-391.55; P = 0.004) and

carriers of the variant allele G in *MUS81* rs545500 displayed decreased EFS (GG vs. CC; HR 4.21; 95% CI 1.20-14.75; P = 0.02 and CG+GG vs. CC; HR 3.73; 95% CI 1.15-12.14, P = 0.03).

**Austrian sample set.** In colon cancer patients, carriers of the variant AA genotype in *REV3L* rs3204953 were associated with decreased OS and EFS in codominant and recessive models (AA vs. GG+GA OS: HR 7.36; 95% CI 11.47-431.53; P < 0.0001 and EFS: HR 7.45; 95% CI 1.75-31.81; P = 0.007). In rectal cancer patients, rs4796033 in the *RAD51D* gene was significantly associated with EFS in the codominant and recessive models (TT vs. CC; HR 9.39; 95% CI 1.13-78.00; P = 0.04 and TT vs. CC+CT; HR 10.86; 95% CI 1.34-88.28; P = 0.03).