Supplementary Table S1. *TP53* mutation spectrum in consensus molecular subtypes (CMS) of colorectal cancer

A *TP53* mutation rate and spectrum in consensus molecular subtypes (CMS) of colorectal cancer among patients from the in-house series.

		Total	CMS1	CMS2	CMS3	CMS4	*P* value[a]
Mutation rate							
	***TP53* wt**	124 (39)	44 (71)	29 (21)	29 (54)	22 (35)	**<0.001**
	***TP53* mut**	192 (61)	18 (29)	109 (79)	25 (46)	40 (65)	
	TOTAL:	316	62	138	54	62	
Type of mutation							
	Missense	128 (67)	15 (83)	68 (62)	17 (68)	28 (70)	0.578
	Nonsense	20 (10)	0	16 (15)	1 (4)	3 (8)	
	Frameshift	27 (14)	2 (11)	15 (14)	3 (12)	7 (18)	
	Indel, in-frame	1 (1)	0	1 (1)	0	0	
	Silent	3 (2)	0	1 (1)	2 (8)	0	
	Splice	13 (7)	1 (6)	8 (7)	2 (8)	2 (5)	
	TOTAL:	192	18	109	25	40	
Functional domain[b]							
	TAD 1/2:	5 (3)	0	0	0	5 (13)	**0.001**
	Proline-rich:	2 (1)	1 (6)	0	0	1 (3)	
	DBD:	166 (93)	15 (88)	97 (96)	22 (96)	32 (84)	
	NLS:	1 (1)	0	0	1 (4)	0	
	OD:	3 (2)	0	3 (3)	0	0	
	Neg:	1 (1)	1 (6)	0	0	0	
	NA:	1 (1)	0	1 (1)	0	0	
	TOTAL:	179	17	101	23	38	

[a] Fisher's exact test. Significant P values in bold.

[b] Excludes splice mutations, as the functional domains are defined according to codon numbers

B *TP53* mutation rate in CMS subtypes, MSS tumors only.

		Total	CMS1	CMS2	CMS3	CMS4	*P* value[a]
Mutation rate	***TP53* wt**	72 (29)	6 (38)	29 (22)	18 (44)	19 (32)	**<0.026**
	***TP53* mut**	179 (71)	10 (63)	106 (79)	23 (56)	40 (68)	
	TOTAL:	251	16	135	41	59	

[a] Fisher's exact test

Supplementary Table S2. Gene Set Enrichment Analysis in *TP53* wild-type and mutated tumors according to consensus molecular subtype.

Results from gene set enrichment analysis using the 50 "hallmark gene sets" from the Molecular Signatures Database (MSigDB 5.2)[1] and performed by the camera R package [2]. *TP53* wild-type tumors were compared with mutated tumors in the four CMS subgroups separately. Analysis performed on 316 tumor samples from the in-house series. Only gene sets displaying significant over- or under-enrichment, as measured by FDR (significance threshold <0.05), are shown here. No significant gene set enrichment between *TP53* wild-type and mutated tumors was found within CMS2. Gene sets are ranked according to adjusted P-values (i.e. FDR-values) with the most significant first.

CMS1

Gene set	Genes (*N*)	Direction[a]	*P* value	FDR
ALLOGRAFT_REJECTION	192	Down	4.41E-13	2.20E-11
INTERFERON_GAMMA_RESPONSE	186	Down	2.68E-12	6.70E-11
INTERFERON_ALPHA_RESPONSE	91	Down	1.01E-07	1.68E-06
OXIDATIVE_PHOSPHORYLATION	184	Down	1.37E-07	1.71E-06
E2F_TARGETS	192	Down	1.37E-06	1.37E-05
G2M_CHECKPOINT	189	Down	5.76E-06	4.80E-05
KRAS_SIGNALING_DN	182	Up	1.11E-04	7.90E-04
IL6_JAK_STAT3_SIGNALING	82	Down	5.27E-04	3.29E-03
INFLAMMATORY_RESPONSE	197	Down	6.67E-04	3.70E-03
MITOTIC_SPINDLE	193	Down	1.09E-03	5.35E-03
COMPLEMENT	188	Down	1.28E-03	5.35E-03
MYC_TARGETS_V1	183	Down	1.25E-03	5.35E-03
MTORC1_SIGNALING	191	Down	1.90E-03	7.30E-03
ADIPOGENESIS	187	Down	2.61E-03	9.32E-03
IL2_STAT5_SIGNALING	192	Down	5.90E-03	1.97E-02
HEDGEHOG_SIGNALING	34	Up	6.85E-03	2.14E-02
MYOGENESIS	192	Up	9.82E-03	2.73E-02
UNFOLDED_PROTEIN_RESPONSE	106	Down	9.33E-03	2.73E-02
PANCREAS_BETA_CELLS	40	Up	1.20E-02	3.17E-02
APOPTOSIS	157	Down	1.72E-02	4.29E-02

CMS3

Gene set	Genes (*N*)	Direction	*P* value	FDR
MTORC1_SIGNALING	191	Down	5.6E-07	2.8E-05
MYC_TARGETS_V1	183	Down	8.7E-04	2.1E-02
GLYCOLYSIS	192	Down	1.3E-03	2.1E-02
INTERFERON_ALPHA_RESPONSE	91	Down	2.4E-03	2.9E-02
INTERFERON_GAMMA_RESPONSE	186	Down	5.1E-03	4.2E-02
UNFOLDED_PROTEIN_RESPONSE	106	Down	4.4E-03	4.2E-02
PROTEIN_SECRETION	93	Down	6.8E-03	4.9E-02

CMS4

Gene set	Genes (*N*)	Direction	*P* value	FDR
E2F_TARGETS	192	Up	1.69E-23	8.46E-22
G2M_CHECKPOINT	189	Up	1.25E-18	3.13E-17
MYC_TARGETS_V1	183	Up	8.46E-17	1.41E-15
MYC_TARGETS_V2	54	Up	9.05E-12	1.13E-10
EPITHELIAL_MESENCHYMAL_TRANSITION	195	Down	3.15E-11	3.15E-10
TNFA_SIGNALING_VIA_NFKB	193	Down	4.93E-09	4.11E-08
ALLOGRAFT_REJECTION	192	Down	1.47E-07	1.05E-06
INFLAMMATORY_RESPONSE	197	Down	2.35E-07	1.47E-06
DNA_REPAIR	136	Up	6.02E-05	3.34E-04
MITOTIC_SPINDLE	193	Up	6.82E-05	3.41E-04
OXIDATIVE_PHOSPHORYLATION	184	Up	7.76E-05	3.53E-04
COMPLEMENT	188	Down	1.92E-04	8.01E-04
KRAS_SIGNALING_DN	182	Down	3.38E-04	1.30E-03
IL6_JAK_STAT3_SIGNALING	82	Down	6.10E-04	2.18E-03
HYPOXIA	188	Down	1.46E-03	4.58E-03
MYOGENESIS	192	Down	1.40E-03	4.58E-03
COAGULATION	131	Down	2.38E-03	7.00E-03
INTERFERON_GAMMA_RESPONSE	186	Down	3.29E-03	8.67E-03
IL2_STAT5_SIGNALING	192	Down	3.21E-03	8.67E-03
KRAS_SIGNALING_UP	187	Down	4.30E-03	1.08E-02
MTORC1_SIGNALING	191	Up	4.76E-03	1.13E-02
ANGIOGENESIS	33	Down	5.49E-03	1.25E-02
ADIPOGENESIS	187	Up	1.27E-02	2.76E-02
APOPTOSIS	157	Down	2.30E-02	4.80E-02

Supplementary Table S3. Immune cell infiltration according to *TP53* mutation status within MSS and MSI tumors

Comparison of differences in abundance of ten different immune and stromal cell populations between *TP53* wild-type and mutated tumors in MSS and MSI tumors. Analysis performed on 316 patients with confident CMS classification from the in-house series.

	MSS (*N*=251)		MSI (*N* =60)	
Cell population	**Mean difference[a]**	***P* value[b]**	**Mean difference [a]**	***P* value[b]**
T cells	0.111	0.64	0.337	0.96
CD8 T cells	0.096	0.22	0.056	1.0
Cytotoxic lymphocytes	0.136	0.34	0.48	0.1
NK cells	0.117	**0.007**	0.143	1.0
B lineage	0.109	1.0	0.162	1.0
Monocytic lineage	0.154	1.0	0.56	0.52
Myeloid dendritic cells	0.101	0.7	0.188	1.0
Neutrophils	0.143	**0.048**	0.116	1.0
Endothelial cells	-0.008	1.0	0.002	1.0
Fibroblasts	0.153	1.0	0.319	1.0

[a]Difference in abundances of relevant cell population between *TP53* wild-type and mutated tumors, as measured by the MCP-counter method.

[b]Independent samples T-test. P values have been multiplied by 20 to account for multiple hypotheses testing according to Bonferroni.

Supplementary Table S4. Immune cell infiltration quantified by multiplex immunohistochemistry according to *TP53* mutation status within the consensus molecular subtypes

Comparison of differences in abundance of CD3+, CD8+ and CD56+ (NK cells) cells between *TP53* wild-type and mutated tumors in CMS1-4. Analysis performed on 230 patients with confident CMS classification and multiplex immunohistochemistry-based quantification of immune cells from the in-house series.

	CMS1 (*N*=45)		CMS2 (*N*=103)		CMS3 (*N*=39)		CMS4 (*N*=43)	
Cell population	**Mean difference[a]**	***P* value[b]**	**Mean difference**	***P* value**	**Mean difference**	***P* value**	**Mean difference**	***P* value**
CD8+ cells	0.088	**0.012**	-0.007	1.0	0.021	1.0	0.007	1.0
CD3+ cells	0.07	1.0	0.002	1.0	0.019	1.0	0.006	1.0
CD56+ cells	0.004	1.0	0.005	1.0	0.011	1.0	-0.001	1.0

[a] Cell positivity fraction for each cell population was calculated for each sample by dividing the number of cells staining for the relevant marker by the total number of cells in the sample. This yields a number between 0 and 1, representing the fraction of relevant immune cell to all cells.

[b]Difference in abundances of relevant cell population between *TP53* wild-type and mutated tumors, as measured by multiplex immmunohistochemistry.

[c]Independent samples T-test. P values have been multiplied by 12 to account for multiple hypotheses testing according to Bonferroni.

Supplementary Table S5. Enrichment of metastatic disease in *TP53* mutated MSS tumors in CMS1

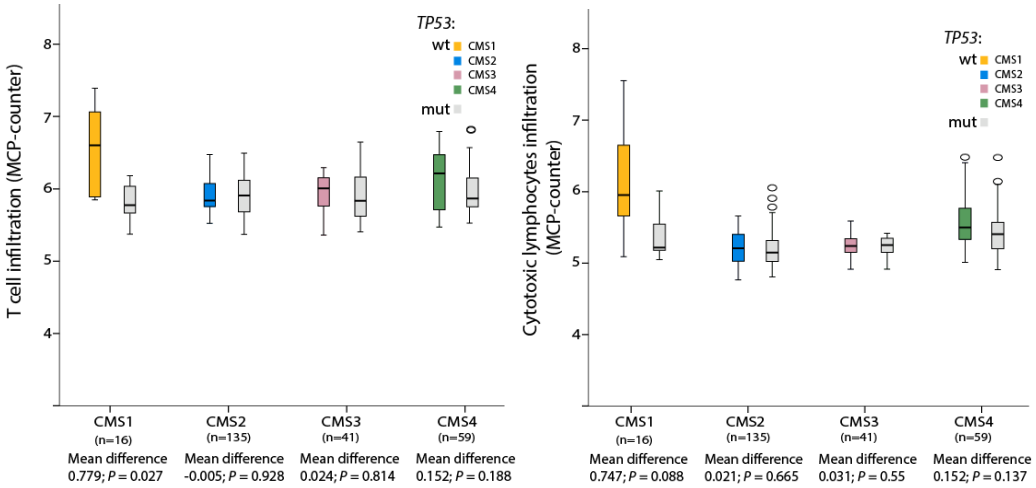
Comparison of the frequency of metastatic disease according to *TP53* mutation status in different strata. Analysis performed on patients with relevant molecular characteristics from the combined patient cohorts.

Molecular characteristic	*N*	Number of patients with metastatic disease (%)	*P*
MSS CMS1			
TP53 mut	18	7 (39)	**0.009**
TP53 wild-type	15	0	
MSI CMS1			
TP53 mut	13	0	1
TP53 wild-type	58	3 (5)	
MSS CMS2-4			
TP53 mut	319	37 (12)	0.572
TP53 wild-type	180	24 (13)	
MSI CMS2-4			
TP53 mut	4	1 (25)	0.324
TP53 wild-type	19	1 (5)	

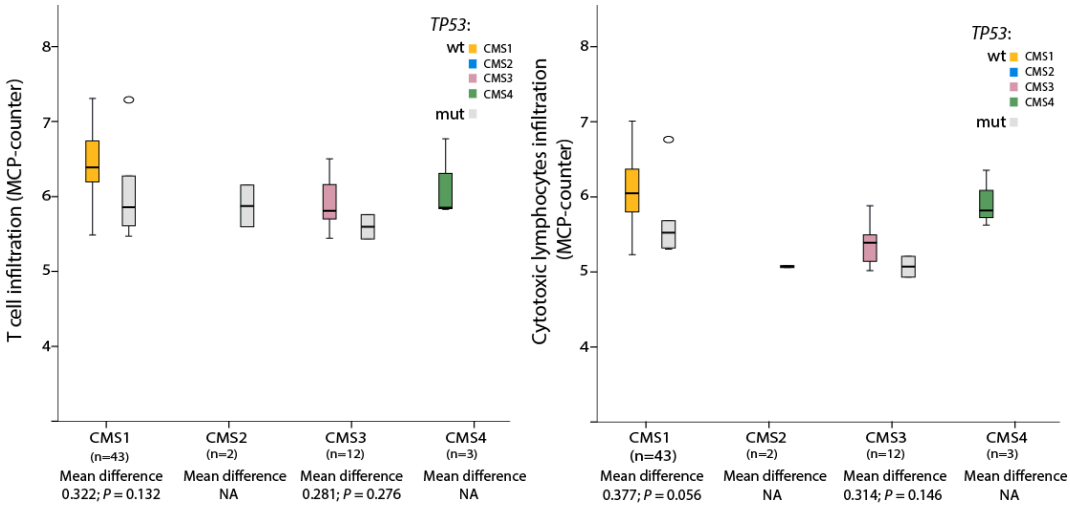
[a] Fisher's exact test

Supplementary Figure S1. Immune cell infiltration according to *TP53* mutation status according to CMS classification and MSI status

MSS



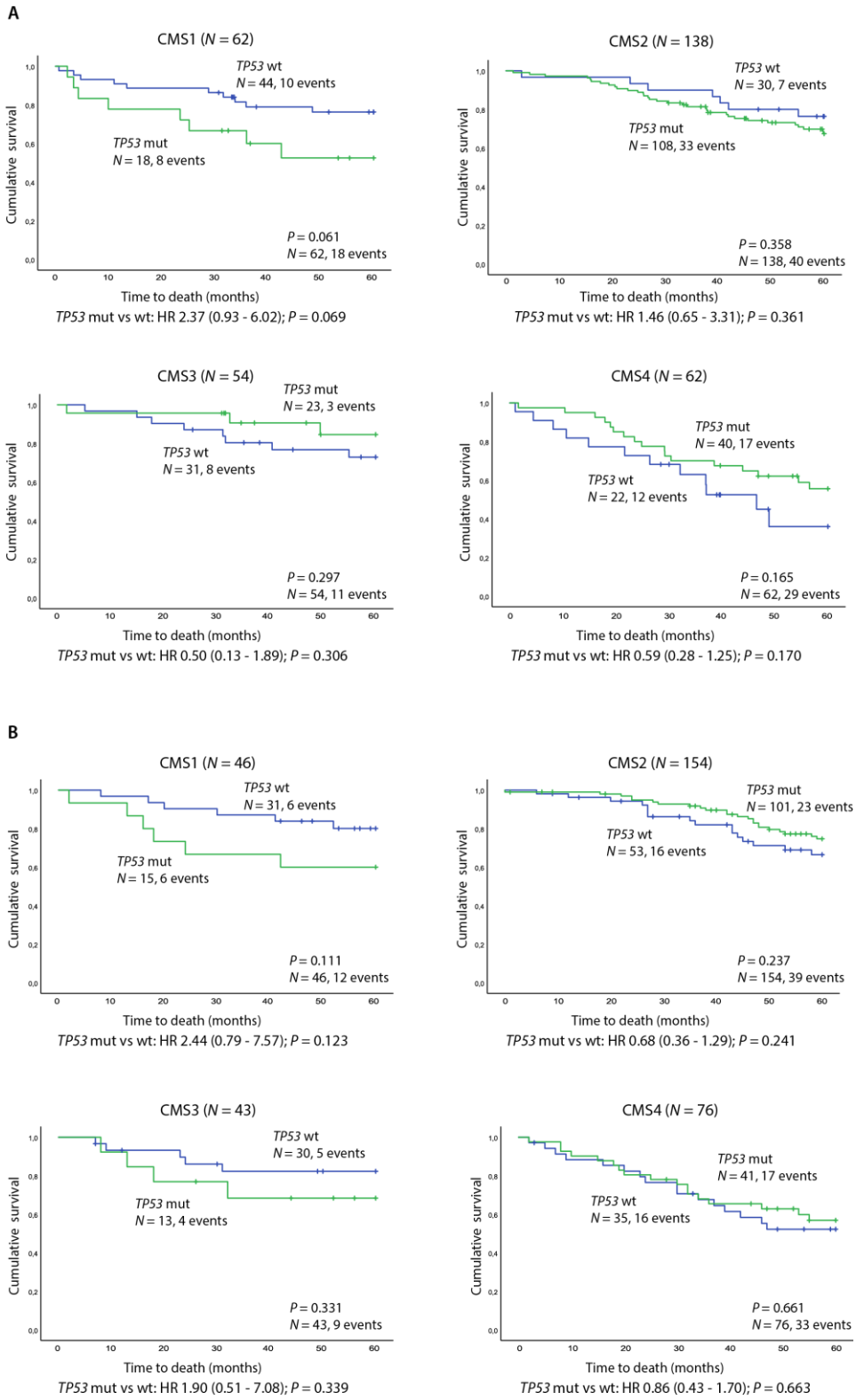
MSI



Comparison of differences in abundance of T cells and cytotoxic lymphocytes in *TP53* wild-type and mutated tumors in CMS1-4 according to MSI status. Abundances of the various cell populations are estimated by applying the MCP-counter method on gene expression data. Analysis performed on 316 patients with confident CMS classification from the in-house series. Unadjusted p-values from independent samples T-test.

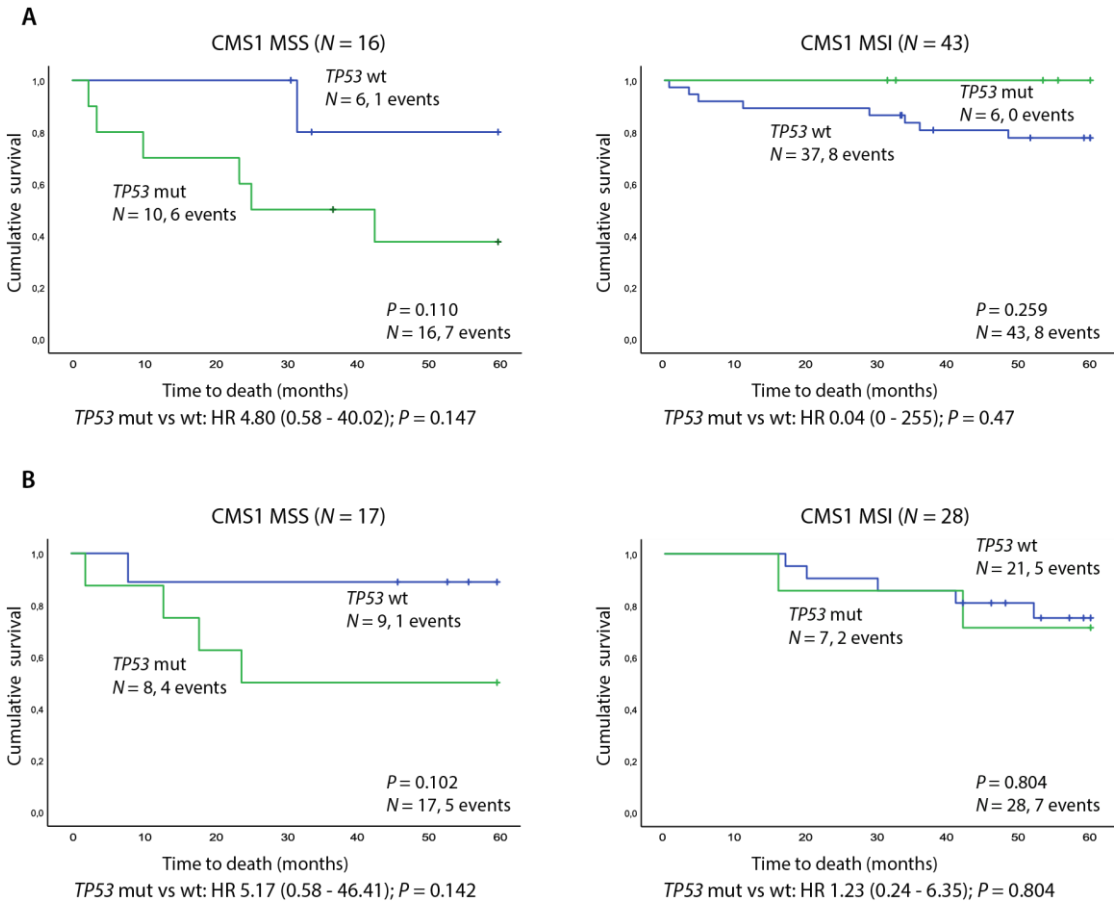
Supplementary Figure S2. Prognostic impact of *TP53* mutations according to the consensus molecular subtype in the independent patient series

Kaplan-Meier survival curves showing 5 year overall survival (OS) according to *TP53* mutation status within the consensus molecular subtypes in the A) in-house (Oslo) series and B) the French multicentre cohort.



Supplementary Figure S3. Prognostic impact of *TP53* mutations in CMS1 stratified according to MSI status in the independent patient series

Kaplan-Meier survival curves comparing *TP53* wild-type and mutated tumors according to MSI status in patients with CMS1 tumors A) in-house (Oslo) series and B) the French multicentre cohort.



Supplementary Figure S4. Prognostic impact of *TP53* mutations in CMS1 MSS tumors according disease stage

Kaplan-Meier survival curves showing 5 year overall survival (OS) according to *TP53* mutation status in CMS1 MSS tumors, stratified into stage I-III and stage IV disease. Analysis performed on patients with the relevant molecular characteristics in the combined patient cohorts.