

Figure S1. Differences in methylation status between specimens taken from metastases compared to specimens from primary tumors. (A) Principal component analysis (PCA) of methylation levels of 417 CpGs from metastases samples (red) and primary tumors (blue). (B) Differences in methylation levels (delta beta) between R and NR (x-axis) might be explained (confounded) by differences in methylation levels (delta beta) between metastases samples (METAST) and primary tumors (PRIM) (y-axis) (orange).

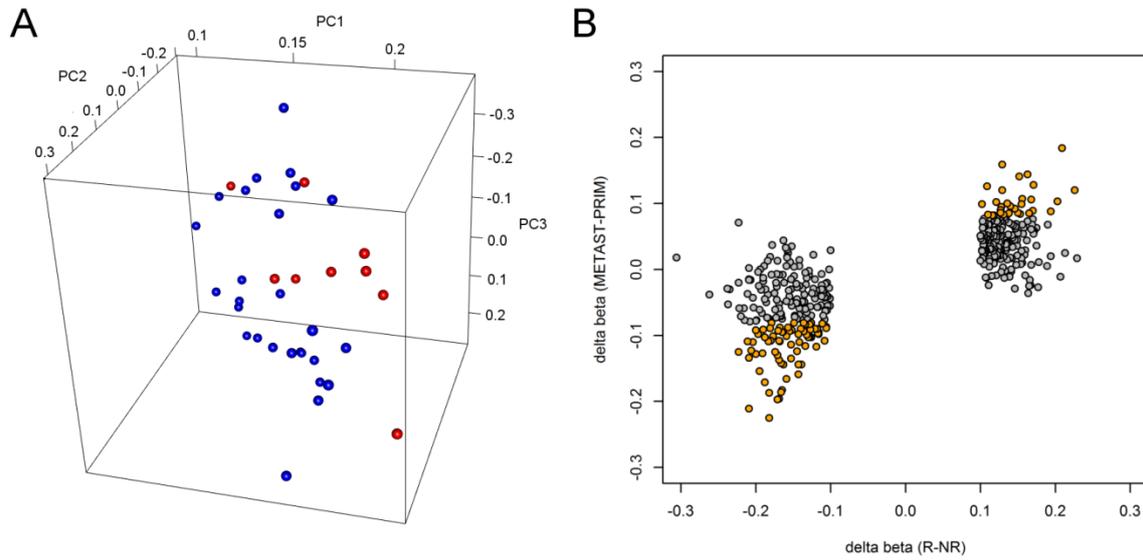


Figure S2. Unsupervised hierarchical clustering of the learning set based on the methylation status (z-score of β -values) of the **48 genes** (48 CpGs) selected for further validation in the optimization set and control set, respectively. This panel allowed a good separation between R (Cluster A + Cluster B) and NR (Cluster C) with an odds ratio of 101 ($P < 0.0001$).

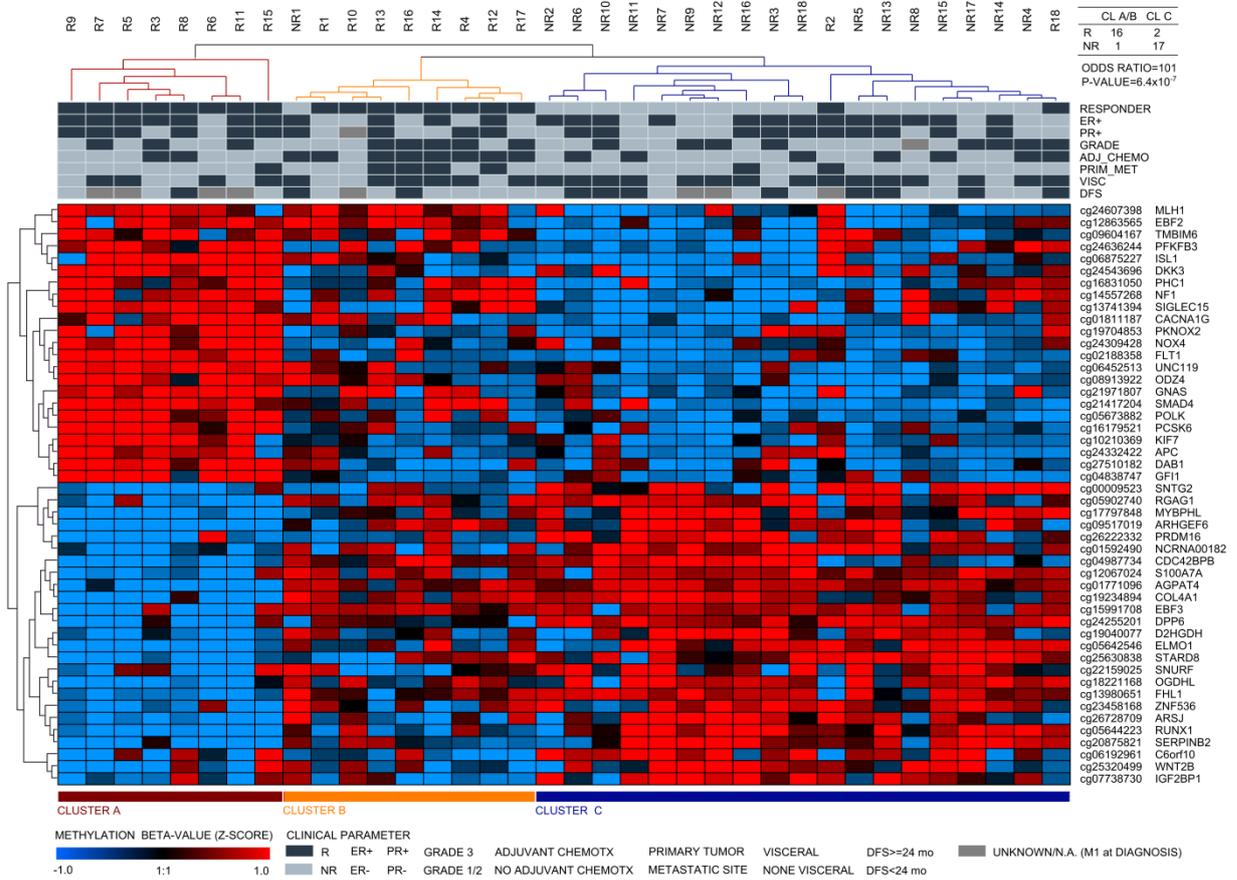


Figure S3. Progression-free survival (PFS) and overall survival (OS) for predicted R and predicted NR according to the **9-gene methylation signature** in the optimization set.

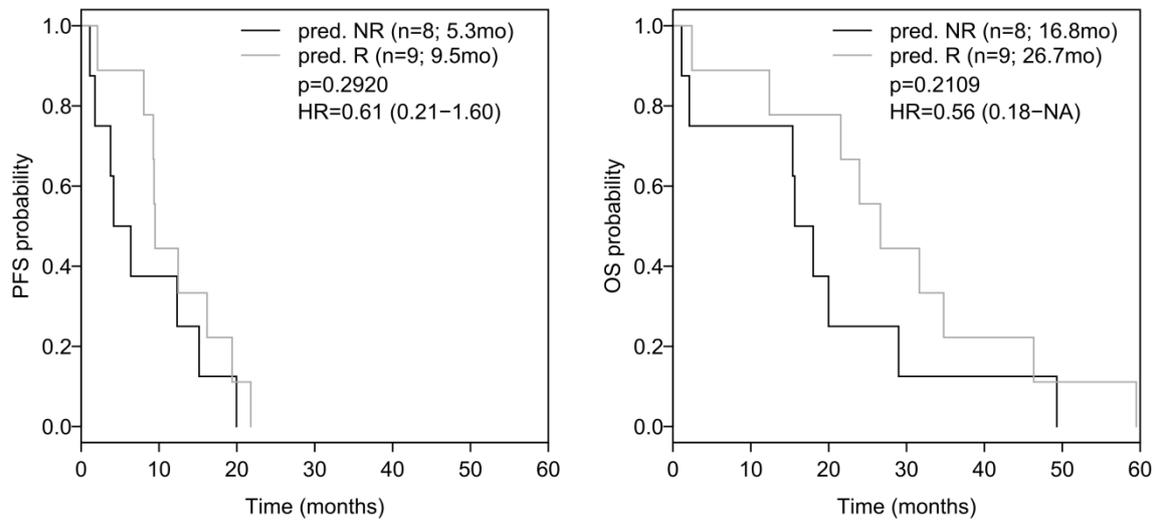


Table S1. Selection methods and genomic position for each of the **48 genes** (48 CpGs) selected for further validation in the *optimization set* and *control set*.

Gene	Probe-ID	Chr	Position	Feature relation	Delta beta	IMA/DMR	LR (AUC>0.85)	Biology
ISL1	cg06875227	5	50683378	Body_island	0.240	1	1	0
SMAD4	cg21417204	18	48609268	3'UTR_none	0.230	1	0	1
GNAS	cg21971807	20	57471654	Body_shelf	0.213	0	1	1
M6PR	cg16831050	12	9093884	3'UTR_none	0.194	1	1	0
TMBIM6	cg09604167	12	50134882	TSS1500_shore	0.180	0	1	1
PFKFB3	cg24636244	10	6221185	Body_none	0.152	0	1	1
POLK	cg05673882	5	74862702	Body_none	0.251	1	0	0
MLH1	cg24607398	3	37033625	1stExon_shore	0.233	0	0	1
EBF2	cg12863565	8	25902558	TSS200_island	0.215	1	1	0
NF1	cg14557268	17	29596696	Body_none	0.201	0	0	1
PCSK6	cg16179521	15	102009894	Body_none	0.192	0	1	0
NOX4	cg24309428	11	89224381	1stExon_shore	0.191	0	1	0
FLT1	cg02188358	13	29068150	Body_island	0.188	0	0	1
PKNOX2	cg19704853	11	125133609	5'UTR_none	0.188	0	1	0
CACNA1G	cg01811187	17	48637445	TSS1500_island	0.184	0	0	1
UNC119	cg06452513	17	26879897	TSS1500_shore	0.150	0	1	0
ODZ4	cg08913922	11	79149704	5'UTR_island	0.257	1*	0	0
KIF7	cg10210369	15	90197924	5'UTR_shore	0.249	0	1	0
SIGLEC15	cg13741394	18	43417389	Body_island	0.219	0	1	0
APC	cg24332422	5	112073686	5'UTR_none	0.208	1	0	1
DKK3	cg24543696	11	12031046	TSS1500_shore	0.172	1	0	1
DAB1	cg27510182	1	58715553	5'UTR_island	0.266	1	0	0
GFI1	cg04838747	1	92950450	5'UTR_island	0.196	1	0	0
EBF3	cg15991708	10	131671760	Body_none	-0.156	1	0	0
ZNF536	cg23458168	19	30864867	5'UTR_shore	-0.210	1*	0	0
OGDHL	cg18221168	10	50971607	TSS1500_shore	-0.213	1*	0	0
S100A7A	cg12067024	1	153387689	TSS1500_none	-0.234	0	1	0
CDC42BPB	cg04987734	14	103415873	Body_none	-0.267	1	1	0
SNTG2	cg00009523	2	1165351	Body_shore	-0.324	0	1	0
SNRPN	cg22159025	15	25201020	5'UTR_island	-0.162	1	0	0
C6orf10	cg06192961	6	32294470	Body_none	-0.206	0	1	0
AGPAT4	cg01771096	6	161638100	Body_none	-0.217	0	1	0
COL4A1	cg19234894	13	110880172	Body_none	-0.219	0	0	1
D2HGDH	cg19040077	2	242702749	Body_none	-0.219	0	1	0
PRDM16	cg26222332	1	3072643	Body_shore	-0.220	0	1	0
ARSJ	cg26728709	4	114823338	3'UTR_none	-0.220	1	0	0
ELMO1	cg05642546	7	37298927	Body_none	-0.222	0	1	1
DPP6	cg24255201	7	154684926	3'UTR_shore	-0.228	0	1	0
MYBPHL	cg17797848	1	109842096	Body_none	-0.251	1	0	0
RGAG1	cg05902740	X	109698667	3'UTR_none	-0.154	1	1	0
FHL1	cg13980651	X	135233206	Body_shelf	-0.156	1	1	0
ARHGEF6	cg09517019	X	135863323	5'UTR_none	-0.162	0	1	1
NCRNA00182	cg01592490	X	73325026	Body_shore	-0.171	1	1	0
STARD8	cg25630838	X	67913165	TSS1500_shore	-0.178	0	1	1
RUNX1	cg05644223	21	36412119	TSS1500_none	-0.235	1	0	1
SERPINB2	cg20875821	18	61557735	5'UTR_none	-0.276	1	1	0
WNT2B	cg25320499	1	113052563	Body_shore	-0.156	1	1	1
IGF2BP1	cg07738730	17	47077165	Body_shore	-0.187	1	1	1

* significantly demethylated regions in R versus NR including all samples (tumor and metastasis)

There are two types of information given for the respective CpG: 1. position in relation to the gene (1stExon: within 1st exon of the gene, 3'UTR: within 3' untranslated region, 5'UTR: within 5' untranslated region, Body: within remaining exons or introns of that gene, TSS1500: within 1500 bp upstream of the transcription start site, TSS200 within 200 bp upstream of the transcription start site) and 2. position in relation to a CpG island (island: within a CpG island, shelf: within ~4 Kb from a CpG island, shore: within ~2 Kb from a CpG island, none: >4kb away from a CpG island).

Table S2. 26 of 48 gene regions presenting CpGs significantly ($p < 0.05$) associated with progression free survival (PFS) or overall survival (OS) or with an area under curve (AUC) > 0.7 from receiver operating characteristics separating responders (*R*) from non-responders (*NR*) in the *optimization set* (chemotherapy plus bevacizumab). These CpG-sites did not show any significant association with PFS in the *control set* (chemotherapy alone), except 5 single CpG sites, where the Hazard ratio showed in the opposite direction (marked in grey).

CHR	POSITION	GENE	Optimization set					Control set	
			PFS		OS		AUC	PFS	
			HR10	P	HR10	P		HR10	P
chr1	58715653	DAB1	0.82	0.1891	0.68	0.0309	0.81	3.25	0.0348
chr1	92950472	GFI1	0.82	0.0073	0.79	0.0044	0.54	1.50	0.0459
chr1	92950478	GFI1	0.81	0.0067	0.80	0.0058	0.54	1.74	0.0259
chr1	92950480	GFI1	0.83	0.0178	0.79	0.0055	0.54	2.19	0.0219
chr1	92950560	GFI1	1.00	0.9849	0.98	0.8515	0.74	2.48	0.0375
chr1	113052446	WNT2B	0.98	0.9007	0.87	0.3691	0.74	1.36	0.3921
chr1	113052487	WNT2B	0.98	0.7963	1.03	0.7531	0.74	1.03	0.9026
chr1	113052544	WNT2B	1.01	0.9443	0.98	0.7775	0.85	0.97	0.8265
chr1	153387609	S100A7A	1.20	0.0127	1.22	0.0106	0.61	0.89	0.4942
chr1	153387661	S100A7A	1.38	0.0011	1.35	0.0025	0.66	0.93	0.7720
chr1	153387689	S100A7A	1.16	0.0489	1.17	0.0311	0.57	0.89	0.5018
chr2	1165409	SNTG2	1.12	0.0883	1.14	0.0477	0.64	0.89	0.5633
chr3	37033489	MLH1	0.86	0.0353	0.87	0.0553	0.82	0.88	0.4677
chr3	37033600	MLH1	0.91	0.1270	0.93	0.2475	0.76	1.01	0.9575
chr3	37033625	MLH1	0.80	0.0039	0.85	0.0246	0.73	0.78	0.3365
chr3	37033632	MLH1	0.86	0.0146	0.87	0.0274	0.73	0.91	0.6652
chr3	37033662	MLH1	0.83	0.0228	0.88	0.0849	0.72	0.99	0.9479
chr4	114823338	ARSJ	1.22	0.0480	1.25	0.0241	0.55	0.92	0.6552
chr4	114823347	ARSJ	1.20	0.0795	1.23	0.0433	0.53	0.90	0.5988
chr5	74862630	POLK	0.77	0.0001	0.80	0.0009	0.66	1.14	0.4531
chr5	74862640	POLK	0.76	0.0001	0.83	0.0069	0.72	1.20	0.3528
chr5	74862646	POLK	0.78	0.0004	0.82	0.0041	0.65	1.11	0.4619
chr5	74862658	POLK	0.80	0.0013	0.84	0.0103	0.62	1.18	0.2869
chr5	74862702	POLK	0.87	0.0344	0.88	0.0527	0.50	1.91	0.0577
chr5	112073686	APC	0.87	0.0385	0.88	0.0657	0.51	1.23	0.1245
chr7	37298864	ELMO1	1.15	0.1131	1.20	0.0371	0.62	0.79	0.1751
chr7	154684831	DPP6	1.10	0.2670	1.10	0.3421	0.73	0.64	0.1048
chr10	131671776	EBF3	1.07	0.2163	1.13	0.0459	0.55	0.96	0.7753
chr10	131671849	EBF3	1.09	0.1623	1.14	0.0390	0.51	0.88	0.5308
chr11	12031097	DKK3	0.86	0.0267	0.89	0.0741	0.52	1.04	0.8212
chr11	12031099	DKK3	0.86	0.0254	0.91	0.1212	0.51	1.16	0.4173
chr11	12031113	DKK3	0.87	0.0322	0.90	0.0850	0.50	0.94	0.7656
chr11	12031148	DKK3	0.81	0.0330	0.93	0.4216	0.55	0.83	0.5669
chr11	79149578	ODZ4	0.84	0.1003	0.80	0.0404	0.61	1.09	0.8291
chr11	79149584	ODZ4	0.89	0.2337	0.77	0.0288	0.60	2.10	0.1253
chr11	89224417	NOX4	0.91	0.1194	0.88	0.0440	0.68	1.05	0.7361
chr11	89224420	NOX4	0.95	0.3956	0.88	0.0442	0.55	0.98	0.9243
chr12	50134851	TMBIM6	0.83	0.0069	0.82	0.0041	0.73	1.00	0.9895
chr13	29068150	FLT1	1.06	0.3361	1.03	0.6797	0.72	1.12	0.4251
chr13	110880253	COL4A1	1.26	0.0478	1.20	0.1168	0.56	0.89	0.5589
chr14	103415861	CDC42BPB	0.84	0.0463	0.88	0.1269	0.51	1.01	0.9389
chr15	25200853	SNRPN	1.16	0.0746	1.20	0.0399	0.66	1.05	0.8432
chr15	25200916	SNRPN	1.16	0.0811	1.19	0.0451	0.66	0.97	0.8920
chr15	25200919	SNRPN	1.18	0.0474	1.22	0.0172	0.63	1.00	0.9870
chr15	25200935	SNRPN	1.19	0.0495	1.21	0.0324	0.70	0.99	0.9612
chr15	25200964	SNRPN	1.22	0.0235	1.20	0.0376	0.74	0.98	0.9402
chr15	25201053	SNRPN	1.10	0.1656	1.15	0.0363	0.52	0.94	0.7058
chr15	90197905	KIF7	0.94	0.2946	0.93	0.2446	0.73	1.09	0.7882
chr15	90198009	KIF7	1.18	0.4839	1.41	0.1542	0.74	0.77	0.6708
chr15	90198067	KIF7	1.10	0.5194	0.98	0.8618	0.72	0.72	0.3541
chr15	102009885	PCSK6	0.87	0.0378	0.84	0.0138	0.51	1.05	0.8756

chr17	26879866	UNC119	0.84	0.0439	0.97	0.6707	0.61	1.22	0.2384
chr18	43417235	SIGLEC15	0.83	0.0440	0.85	0.1053	0.68	0.85	0.4160
chr18	43417241	SIGLEC15	0.76	0.0186	0.74	0.0151	0.68	0.96	0.8412
chr20	57471607	GNAS	0.81	0.0004	0.89	0.0343	0.70	0.93	0.5070
chr20	57471654	GNAS	0.82	0.0042	0.79	0.0003	0.60	1.03	0.8542
chr20	57471660	GNAS	0.83	0.0021	0.84	0.0015	0.63	1.03	0.8533
chr20	57471672	GNAS	0.82	0.0041	0.82	0.0011	0.51	1.02	0.9169
chr20	57471758	GNAS	0.79	0.0034	0.79	0.0019	0.57	1.14	0.5454

HR10: hazard ratio for 10% rise of methylation; AUC: area under receiver operating characteristics curve; PFS: progression-free survival; OS: overall survival;

Table S3. Selected CpGs for methylation analysis in the **9-gene methylation signature** in the *learning set* and in the *optimization set* (3 gene methylation signature is indicated by *)

GENE	LEARNING SET					OPTIMIZATION SET			
	CG ID	CHR	POS	R-NR	AUC	CHR	POS	R-NR	AUC
<i>WNT2B</i>	cg25320499	chr1	113052563	-0.132	0.81	chr1	113052544	-0.186	0.85
<i>MLH1*</i>	cg24607398	chr3	37033625	0.216	0.81	chr3	37033625	0.173	0.73
<i>POLK*</i>	cg05673882	chr5	74862702	0.229	0.78	chr5	74862640	0.098	0.72
<i>NOX4</i>	cg24309428	chr11	89224381	0.160	0.81	chr11	89224417	0.192	0.68
<i>PKNOX2</i>	cg19704853	chr11	125133609	0.159	0.85	chr11	125133601	0.180	0.70
<i>TMBIM6*</i>	cg09604167	chr12	50134882	0.179	0.84	chr12	50134851	0.132	0.73
<i>SNRPN</i>	cg22159025	chr15	25201020	-0.155	0.83	chr15	25200964	-0.143	0.74
<i>UNC119</i>	cg06452513	chr17	26879897	0.144	0.82	chr17	26879897	-0.019	0.55
<i>GNAS</i>	cg21971807	chr20	57471654	0.186	0.80	chr20	57471607	0.190	0.70

CG ID is the identifier from the 450k Illumina methylation arrays; POS is the position in the hg19 genome assembly; R-NR is the mean difference in methylation levels ($\Delta\beta$) from responders *versus* non-responders; AUC area under the receiver operating characteristics curve separating responders from non-responders.

Table S4. Parameters of the logistic regression models of the **9-gene methylation signature** and the **3-gene methylation signature** learned from the data in the learning set.

9-GENE METHYLATION SIGNATURE			3-GENE METHYLATION SIGNATURE		
GENE	COEFFICIENT	LR CUTOFF*	GENE	COEFFICIENT	LR CUTOFF*
<i>Intercept</i>	-14.077		<i>Intercept</i>	-10.558	
<i>WNT2B</i>	-0.546		<i>MLH1</i>	7.953	0.541
<i>MLH1</i>	9.389		<i>POLK</i>	6.403	
<i>POLK</i>	-5.608		<i>TMBIM6</i>	9.864	
<i>NOX4</i>	8.428	0.725			
<i>PKNOX2</i>	13.273				
<i>TMBIM6</i>	17.502				
<i>SNRPN</i>	-3.942				
<i>UNC119</i>	0.416				
<i>GNAS</i>	0.052				

*LR cutoff is the optimized cutoff from the ROC curve analysis from the respective logistic regression model with p>cutoff is predicted responder