



**Figure S1** Copy number alterations at different locations in the primary tumors from the LuM and LiM cohorts. LuM, lung metastases; LiM, liver metastases; AMP, amplification.

**Table S1** Single nucleotide variations in the primary tumors from the LuM, LiM and control cohorts, n (%)

Gene	LuM + LiM	Control	P	LuM	LiM	P
	n=32	n=10		n=16	n=16	
<i>TP53</i>	20 (62.5)	9 (90.0)	0.211	11 (68.8)	9 (56.3)	0.716
<i>APC</i>	17 (53.1)	8 (80.0)	0.253	9 (56.3)	10 (62.5)	1.000
<i>KRAS</i>	8 (25.0)	2 (20.0)	1.000	6 (37.5)	5 (31.3)	1.000
<i>FBXW7</i>	5 (15.6)	2 (20.0)	1.000	3 (18.8)	2 (12.5)	1.000
<i>PIK3CA</i>	5 (15.6)	1 (10.0)	1.000	4 (25.0)	0 (0.0)	0.101
<i>ALK</i>	3 (9.4)	0 (0.0)	1.000	3 (18.8)	2 (12.5)	1.000
<i>ERBB2</i>	3 (9.4)	0 (0.0)	1.000	3 (18.8)	1 (6.3)	0.600
<i>ERBB3</i>	4 (12.5)	1 (10.0)	1.000	3 (18.8)	0 (0.0)	0.226
<i>RYR2</i>	3 (9.4)	0 (0.0)	1.000	3 (18.8)	1 (6.3)	0.600
<i>IDH1</i>	1 (3.1)	0 (0.0)	1.000	1 (6.3)	2 (12.5)	1.000
<i>HRAS</i>	2 (6.3)	1 (10.0)	1.000	1 (6.3)	1 (6.3)	1.000
<i>TSPYL2</i>	3 (9.4)	0 (0.0)	1.000	3 (18.8)	0 (0.0)	0.226
<i>DST</i>	2 (6.3)	1 (10.0)	1.000	1 (6.3)	1 (6.3)	1.000
<i>GNAS</i>	3 (9.4)	0 (0.0)	1.000	3 (18.8)	0 (0.0)	0.226
<i>SMAD4</i>	3 (9.4)	2 (20.0)	0.729	1 (6.3)	0 (0.0)	1.000
<i>NTRK1</i>	0 (0.0)	0 (0.0)	–	0 (0.0)	3 (18.8)	0.226
<i>LGALS3</i>	3 (9.4)	0 (0.0)	1.000	3 (18.8)	0 (0.0)	0.226
<i>EGFR</i>	2 (6.3)	0 (0.0)	1.000	2 (12.5)	1 (6.3)	1.000
<i>BRD7</i>	2 (6.3)	0 (0.0)	1.000	2 (12.5)	1 (6.3)	1.000
<i>EIF3A</i>	3 (9.4)	0 (0.0)	1.000	3 (18.8)	0 (0.0)	0.226
<i>AMER1</i>	2 (6.3)	1 (10.0)	1.000	1 (6.3)	1 (6.3)	1.000
<i>RNF43</i>	2 (6.3)	0 (0.0)	1.000	2 (12.5)	1 (6.3)	1.000
<i>MEF2B</i>	1 (3.1)	0 (0.0)	1.000	1 (6.3)	2 (12.5)	1.000
<i>TET2</i>	2 (6.3)	0 (0.0)	1.000	2 (12.5)	1 (6.3)	1.000
<i>NRAS</i>	2 (6.3)	1 (10.0)	1.000	1 (6.3)	1 (6.3)	1.000
<i>PRKCB</i>	2 (6.3)	0 (0.0)	1.000	2 (12.5)	1 (6.3)	1.000
<i>PFKFB1</i>	3 (9.4)	0 (0.0)	1.000	3 (18.8)	0 (0.0)	0.226

LuM, lung metastases; LiM, liver metastases.

**Table S2** Copy number variations in the primary tumors from the LuM, LiM and control cohorts, n (%)

Gene	LuM + LiM (n=32)	Control (n=10)	P	LuM (n=16)	LiM (n=16)	P
ZFHX4	29 (90.6)	1 (10.0)	<0.001 <sup>#</sup>	16 (100.0)	13 (81.3)	0.226
GATA2	11 (34.4)	0 (0.0)	0.081	8 (50.0)	3 (18.8)	0.135
FAM131B	11 (34.4)	0 (0.0)	0.081	8 (50.0)	3 (18.8)	0.135
HNF4A	7 (21.9)	4 (40.0)	0.468	7 (43.8)	0 (0.0)	0.007 <sup>#</sup>
RECQL4	2 (6.3)	7 (70.0)	<0.001 <sup>#</sup>	0 (0.0)	2 (12.5)	0.484
FOXL2	9 (28.1)	0 (0.0)	0.147	2 (12.5)	7 (43.8)	0.113
BRD4	9 (28.1)	0 (0.0)	0.147	8 (50.0)	1 (6.3)	0.015 <sup>#</sup>
CEBPA	6 (18.8)	3 (30.0)	0.753	2 (12.5)	4 (25.0)	0.654
KAT6A	8 (25.0)	0 (0.0)	0.195	5 (31.3)	3 (18.8)	0.685
MKI67	8 (25.0)	0 (0.0)	0.195	6 (37.5)	2 (12.5)	0.220
FLT1	6 (18.8)	2 (20.0)	1.000	5 (31.3)	1 (6.3)	0.172
DDR1 *	5 (15.6)	2 (20.0)	1.000	2 (12.5)	3 (18.8)	1.000
NBN	5 (15.6)	2 (20.0)	1.000	2 (12.5)	3 (18.8)	1.000
RIPK2	3 (9.4)	3 (30.0)	0.267	1 (6.3)	2 (12.5)	1.000
RB1	5 (15.6)	1 (10.0)	1.000	3 (18.8)	2 (12.5)	1.000
CYP2A6 *	2 (6.3)	3 (30.0)	0.143	1 (6.3)	1 (6.3)	1.000
HIP1	5 (15.6)	0 (0.0)	0.440	4 (25.0)	1 (6.3)	0.333
U2AF1	5 (15.6)	0 (0.0)	0.440	5 (31.3)	0 (0.0)	0.043 <sup>#</sup>
EP300	5 (15.6)	0 (0.0)	0.440	4 (25.0)	1 (6.3)	0.333
ETV4	5 (15.6)	0 (0.0)	0.440	4 (25.0)	1 (6.3)	0.333
CYP2B6	5 (15.6)	0 (0.0)	0.440	4 (25.0)	1 (6.3)	0.333
CDK8	3 (9.4)	2 (20.0)	0.729	3 (18.8)	0 (0.0)	0.226
SDC4	3 (9.4)	2 (20.0)	0.729	2 (12.5)	1 (6.3)	1.000
CSMD3	4 (12.5)	1 (10.0)	1.000	1 (6.3)	3 (18.8)	0.600
ABCC4	4 (12.5)	1 (10.0)	1.000	3 (18.8)	1 (6.3)	0.600
GLI3	4 (12.5)	1 (10.0)	1.000	3 (18.8)	1 (6.3)	0.600
NFATC2	2 (6.3)	2 (20.0)	0.236	2 (12.5)	0 (0.0)	0.484
SRC	2 (6.3)	2 (20.0)	0.236	2 (12.5)	0 (0.0)	0.484
TRPS1	2 (6.3)	2 (20.0)	0.236	1 (6.3)	1 (6.3)	1.000
MLLT10	4 (12.5)	0 (0.0)	0.557	3 (18.8)	1 (6.3)	0.600
FLT3	4 (12.5)	0 (0.0)	0.557	4 (25.0)	0 (0.0)	0.101
SOX9	4 (12.5)	0 (0.0)	0.557	4 (25.0)	0 (0.0)	0.101
COL1A2	4 (12.5)	0 (0.0)	0.557	3 (18.8)	1 (6.3)	0.600
CYP2D6	3 (9.4)	1 (10.0)	1.000	0 (0.0)	3 (18.8)	0.226
PDPR	3 (9.4)	1 (10.0)	1.000	2 (12.5)	1 (6.3)	1.000
FLCN <sup>&amp;</sup>	0 (0.0)	3 (30.0)	0.010 <sup>#</sup>	0 (0.0)	0 (0.0)	/
ETV1	1 (3.1)	2 (20.0)	0.136	0 (0.0)	1 (6.3)	1.000
TPM3	3 (9.4)	0 (0.0)	1.000	3 (18.8)	0 (0.0)	0.226
ERC1	3 (9.4)	0 (0.0)	1.000	2 (12.5)	1 (6.3)	1.000
CDK12	3 (9.4)	0 (0.0)	1.000	1 (6.3)	2 (12.5)	1.000
ARID1B	3 (9.4)	0 (0.0)	1.000	2 (12.5)	1 (6.3)	1.000
FOXA1*	3 (9.4)	0 (0.0)	1.000	1 (6.3)	2 (12.5)	1.000
FAM135B	2 (6.3)	1 (10.0)	1.000	1 (6.3)	1 (6.3)	1.000
BRC A2	2 (6.3)	1 (10.0)	1.000	2 (12.5)	0 (0.0)	0.484
PLAG1	2 (6.3)	1 (10.0)	1.000	1 (6.3)	1 (6.3)	1.000
KMT2C	3 (9.4)	0 (0.0)	1.000	2 (12.5)	1 (6.3)	1.000
ABCC5	3 (9.4)	0 (0.0)	1.000	1 (6.3)	2 (12.5)	1.000

\*, CNVs included both loss and amplification; <sup>&</sup>, only the FLCN gene showed a loss of copy number. Other genes showed only amplification; <sup>#</sup>, P values <0.05. LuM, lung metastases; LiM, liver metastases.

**Table S3** Alteration frequencies of colorectal cancer pathways and related genes in the primary tumors and metastatic lesions

Pathway	Gene	Primary tumors, n (%)					Metastatic lesions, n (%)		
		LuM cohort (n=16)	LiM cohort (n=16)	Control cohort (n=10)	P <sub>LuM vs. LiM</sub>	P <sub>LuM vs. Control</sub>	LuM cohort (n=15)	LiM cohort (n=18)	P
WNT		10 (62.5)	11 (68.8)	8 (80.0)	1.000	0.420	9 (60.0)	13 (72.2)	0.488
	<i>APC</i>	9 (56.3)	10 (62.5)	8 (80.0)	1.000	0.399	8 (53.3)	12 (66.7)	0.493
	<i>AMER1</i>	1 (6.3)	1 (6.3)	1 (10.0)	1.000	1.000	0 (0.0)	1 (5.6)	1.000
	<i>RNF43</i>	2 (12.5)	1 (6.3)	0 (0.0)	1.000	0.508	1 (6.7)	0 (0.0)	0.455
	<i>CTNNB1</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	1 (6.7)	0 (0.0)	0.455
	<i>GSK3B</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	1 (5.6)	1.000
	<i>SFRP2</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	1 (5.6)	1.000
	<i>TCF7L2</i>	0 (0.0)	0 (0.0)	1 (10.0)	–	0.385	0 (0.0)	0 (0.0)	–
TGFβ		2 (12.5)	3 (18.8)	3 (30.0)	1.000	0.340	4 (26.7)	4 (22.2)	1.000
	<i>SMAD4</i>	1 (6.3)	1 (6.3)	2 (20.0)	1.000	0.538	3 (20.0)	1 (5.6)	0.308
	<i>SMAD2</i>	0 (0.0)	0 (0.0)	1 (10.0)	–	0.385	1 (6.7)	2 (11.1)	1.000
	<i>SMAD3</i>	1 (6.3)	1 (6.3)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
	<i>TGFBR1</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	2 (11.1)	0.489
	<i>ACVR1B</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455
	<i>TGFBR2</i>	0 (0.0)	1 (6.3)	0 (0.0)	1.000	–	0 (0.0)	0 (0.0)	–
RTK/RAS		14 (87.5)	11 (68.8)	7 (70.0)	0.394	0.340	15 (100.0)	13 (72.2)	0.049 <sup>#</sup>
	<i>KRAS</i>	7 (43.8)	5 (31.3)	3 (30.0)	0.716	0.683	11 (73.3)	7 (38.9)	0.080
	<i>EGFR</i>	2 (12.5)	1 (6.3)	1 (10.0)	1.000	1.000	1 (6.7)	4 (22.2)	0.346
	<i>ERBB3</i>	3 (18.8)	0 (0.0)	1 (10.0)	0.226	1.000	2 (13.3)	3 (16.7)	1.000
	<i>NTRK1</i>	2 (12.5)	3 (18.8)	0 (0.0)	1.000	0.508	2 (13.3)	2 (11.1)	1.000
	<i>HRAS</i>	1 (6.3)	1 (6.3)	2 (20.0)	1.000	0.538	3 (20.0)	1 (5.6)	0.308
	<i>ALK</i>	3 (18.8)	2 (12.5)	0 (0.0)	1.000	0.262	0 (0.0)	2 (11.1)	0.489
	<i>MET</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	6 (40.0)	1 (5.6)	0.030 <sup>#</sup>
	<i>ERBB2</i>	3 (18.8)	1 (6.3)	0 (0.0)	0.600	0.262	1 (6.7)	1 (5.6)	1.000
	<i>FLT3</i>	4 (25.0)	0 (0.0)	0 (0.0)	0.101	0.136	0 (0.0)	2 (11.1)	0.489
	<i>KIT</i>	2 (12.5)	0 (0.0)	0 (0.0)	0.484	0.508	2 (13.3)	2 (11.1)	1.000
	<i>NRAS</i>	1 (6.3)	1 (6.3)	1 (10.0)	1.000	1.000	1 (6.7)	1 (5.6)	1.000
	<i>FGFR3</i>	2 (12.5)	0 (0.0)	0 (0.0)	0.484	0.508	1 (6.7)	1 (5.6)	1.000
	<i>BRAF</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	1 (6.7)	1 (5.6)	1.000
	<i>ERBB4</i>	1 (6.3)	0 (0.0)	1 (10.0)	1.000	1.000	0 (0.0)	1 (5.6)	1.000
	<i>FGFR2</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	2 (11.1)	1.000
	<i>MAP2K1</i>	2 (12.5)	0 (0.0)	0 (0.0)	0.484	0.508	1 (6.7)	0 (0.0)	0.455
	<i>NTRK3</i>	1 (6.3)	0 (0.0)	1 (10.0)	1.000	1.000	1 (6.7)	0 (0.0)	0.455
	<i>PDGFRA</i>	2 (12.5)	0 (0.0)	0 (0.0)	0.484	0.508	1 (6.7)	0 (0.0)	0.455
	<i>CBL</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	1 (5.6)	1.000
	<i>NF1</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	2 (13.3)	0 (0.0)	0.199
	<i>PTPN11</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	1 (5.6)	1.000
	<i>RET</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	1 (6.7)	0 (0.0)	0.455
	<i>ARAF</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455
	<i>FGFR1</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	1 (5.6)	1.000
	<i>FGFR4</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
	<i>IGF1R</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
<i>MAP2K2</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455	
<i>MAPK1</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–	
<i>ROS1</i>	0 (0.0)	0 (0.0)	1 (10.0)	–	0.385	0 (0.0)	0 (0.0)	–	
PI3K		8 (50.0)	4 (25.0)	2 (20.0)	0.273	0.218	8 (53.3)	7 (38.9)	0.494
	<i>PIK3CA</i>	4 (25.0)	0 (0.0)	1 (10.0)	0.101	0.617	1 (6.7)	3 (16.7)	0.607
	<i>MTOR</i>	2 (12.5)	0 (0.0)	0 (0.0)	0.484	0.508	0 (0.0)	3 (16.7)	0.233

**Table S3** (continued)

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Pathway	Gene	Primary tumors, n (%)					Metastatic lesions, n (%)		
		LuM cohort (n=16)	LiM cohort (n=16)	Control cohort (n=10)	P <sub>LuM vs. LiM</sub>	P <sub>LuM vs. Control</sub>	LuM cohort (n=15)	LiM cohort (n=18)	P
	<i>STK11</i>	1 (6.3)	0 (0.0)	1 (10.0)	1.000	1.000	2 (13.3)	0 (0.0)	0.199
	<i>TSC1</i>	0 (0.0)	1 (6.3)	0 (0.0)	1.000	–	1 (6.7)	2 (11.1)	1.000
	<i>PPP2R1A</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	2 (13.3)	0 (0.0)	0.199
	<i>PTEN</i>	1 (6.3)	1 (6.3)	0 (0.0)	1.000	1.000	0 (0.0)	1 (5.6)	1.000
	<i>AKT1</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	2 (13.3)	0 (0.0)	0.199
	<i>AKT3</i>	2 (12.5)	0 (0.0)	0 (0.0)	0.484	0.508	0 (0.0)	0 (0.0)	–
	<i>PIK3CB</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	1 (6.7)	0 (0.0)	0.455
	<i>PIK3R1</i>	0 (0.0)	1 (6.3)	0 (0.0)	1.000	–	0 (0.0)	1 (5.6)	1.000
	<i>TSC2</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	1 (6.7)	0 (0.0)	0.455
	<i>PIK3R2</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455
	<i>RICTOR</i>	0 (0.0)	1 (6.3)	0 (0.0)	1.000	–	0 (0.0)	0 (0.0)	–
P53		12 (75.0)	10 (62.5)	9 (90.0)	0.704	0.617	14 (93.3)	12 (66.7)	0.095
	<i>TP53</i>	11 (68.8)	9 (56.3)	9 (90.0)	0.716	0.352	13 (86.7)	12 (66.7)	0.242
	<i>MDM4</i>	2 (12.5)	0 (0.0)	0 (0.0)	0.484	0.508	2 (13.3)	0 (0.0)	0.199
	<i>ATM</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455
	<i>RPS6KA3</i>	0 (0.0)	1 (6.3)	0 (0.0)	1.000	–	0 (0.0)	0 (0.0)	–
NRF2		1 (6.3)	1 (6.3)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
	<i>CUL3</i>	0 (0.0)	1 (6.3)	0 (0.0)	1.000	–	0 (0.0)	0 (0.0)	–
	<i>KEAP1</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
NOTCH		9 (56.3)	6 (37.5)	3 (30.0)	0.479	0.248	7 (46.7)	8 (44.4)	1.000
	<i>FBXW7</i>	3 (18.8)	2 (12.5)	2 (20.0)	1.000	1.000	2 (13.3)	3 (16.7)	1.000
	<i>EP300</i>	4 (25.0)	1 (6.3)	0 (0.0)	0.333	0.136	2 (13.3)	2 (11.1)	1.000
	<i>KDM5A</i>	0 (0.0)	1 (6.3)	0 (0.0)	1.000	–	3 (20.0)	3 (16.7)	1.000
	<i>NOTCH1</i>	1 (6.3)	1 (6.3)	1 (10.0)	1.000	1.000	2 (13.3)	0 (0.0)	0.199
	<i>NOTCH2</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	1 (6.7)	2 (11.1)	1.000
	<i>NOTCH3</i>	1 (6.3)	1 (6.3)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
	<i>SPEN</i>	2 (12.5)	0 (0.0)	0 (0.0)	0.484	0.508	0 (0.0)	0 (0.0)	–
	<i>NCOR1</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
MYC		1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	2 (13.3)	0 (0.0)	0.199
	<i>MAX</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455
	<i>MYCL</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
	<i>MYCN</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455
HIPPO		2 (12.5)	2 (12.5)	0 (0.0)	1.000	0.508	5 (33.3)	1 (5.6)	0.070
	<i>FAT3</i>	0 (0.0)	1 (6.3)	0 (0.0)	1.000	–	3 (20.0)	0 (0.0)	0.083
	<i>FAT4</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	2 (13.3)	1 (5.6)	0.579
	<i>FAT1</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	1 (5.6)	1.000
	<i>FAT2</i>	1 (6.3)	1 (6.3)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
	<i>NF2</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
Cell cycle		5 (31.3)	3 (18.8)	2 (20.0)	0.685	0.668	4 (26.7)	5 (27.8)	1.000
	<i>RB1</i>	4 (25.0)	3 (18.8)	1 (10.0)	1.000	0.617	2 (13.3)	3 (16.7)	1.000
	<i>CDK4</i>	0 (0.0)	0 (0.0)	1 (10.0)	–	0.385	2 (13.3)	0 (0.0)	0.199
	<i>CCND3</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	1 (5.6)	1.000
	<i>CCNE1</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455
	<i>CDKN1A</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455
	<i>CDKN2C</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	1 (6.7)	0 (0.0)	0.455
	<i>E2F1</i>	1 (6.3)	0 (0.0)	0 (0.0)	1.000	1.000	0 (0.0)	0 (0.0)	–
	<i>CDKN2A</i>	0 (0.0)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	1 (5.6)	1.000

# P values <0.05. LuM, lung metastases; LiM, liver metastases.

**Table S4** Comparison of the frequencies of possible gene alterations associated with immune checkpoint inhibitors

Gene alteration	Cohort (n)					P					
	LuM-P (n=16)	LiM-P (n=16)	Control-P (n=10)	LuM-M (n=15)	LiM-M (n=18)	LuM-P vs. LiM-P	LuM-P vs. Control-P	LiM-P vs. Control-P	LuM-M vs. LiM-M	LuM-P vs. LuM-M	LiM-P vs. LiM-M
<i>TP53</i>											
Mutation											
+	11	9	9	13	12	0.716	0.352	0.099	0.242	0.394	0.725
-	5	7	1	2	6						
<i>KRAS</i>											
Mutation											
+	6	5	2	9	7	1	0.42	0.668	0.303	0.289	0.729
-	10	11	8	6	11						
<i>NRAS</i>											
Mutation											
+	1	1	1	1	1	1	1	1	1	1	1
-	15	15	9	14	17						
<i>ERCC2</i>											
Mutation											
+	0	2	0	3	0	0.484	-	0.508	0.083	0.101	0.214
-	16	14	10	12	18						
<i>POLE</i>											
Loss											
+	0	0	1	0	0	-	0.385	0.385	-	-	-
-	16	16	9	15	18						
Mutation											
+	1	1	0	1	0	1	1	1	0.455	1	0.471
-	15	15	10	14	18						
<i>MLH1</i>											
Mutation											
+	1	1	0	1	1	1	1	1	1	1	1
-	15	15	10	14	17						
<i>PMS2</i>											
Mutation											
+	2	0	0	1	0	0.484	0.508	-	0.455	1	-
-	14	16	10	14	18						
<i>MSH6</i>											
Mutation											
+	2	0	0	0	0	0.484	0.508	-	-	0.484	-
-	14	16	10	15	18						
<i>BRCA2</i>											
Mutation											
+	0	0	0	1	1	-	-	-	1	1	1
-	16	16	10	14	17						
<i>MDM4</i>											
Gain											
+	1	0	0	1	0	1	1	-	0.455	1	-
-	15	16	10	14	18						
<i>PBRM1</i>											
Mutation											
+	1	0	0	0	0	1	1	-	-	1	-
-	15	16	10	15	18						

**Table S4** (continued)

Table S4 (continued)

Gene alteration	Cohort (n)					P					
	LuM-P (n=16)	LiM-P (n=16)	Control-P (n=10)	LuM-M (n=15)	LiM-M (n=18)	LuM-P vs. LiM-P	LuM-P vs. Control-P	LiM-P vs. Control-P	LuM-M vs. LiM-M	LuM-P vs. LuM-M	LiM-P vs. LiM-M
<i>BRCA1</i>											
Mutation											
+	0	0	0	0	1	-	-	-	1	-	1
-	16	16	10	15	17						
<i>ATM</i>											
Mutation											
+	0	0	0	1	0	-	-	-	0.455	1	-
-	16	16	10	14	18						
<i>EGFR</i>											
Gain											
+	0	0	1	1	1	-	0.385	0.385	1	0.484	1
-	16	16	9	14	17						
Mutation											
+	2	1	0	0	3	1	0.508	1	0.233	0.484	0.604
-	14	15	10	15	15						
<i>STK11</i>											
Mutation											
+	1	0	0	2	0	1	1	-	0.199	0.6	-
-	15	16	10	13	18						
<i>MET</i>											
Mutation											
+	0	0	0	2	1	-	-	-	0.579	0.226	1
-	16	16	10	13	17						
<i>CTNNB1</i>											
Mutation											
+	1	0	0	1	0	1	1	-	0.455	1	-
-	15	16	10	14	18						
<i>JAK1</i>											
Mutation											
+	0	0	0	1	0	-	-	-	0.455	1	-
-	16	16	10	14	18						
<i>PTEN</i>											
Loss											
+	0	0	0	0	1	-	-	-	1	-	1
-	16	16	10	15	17						

LuM, lung metastases; LiM, liver metastases; P, primary tumor; M, metastatic lesion.