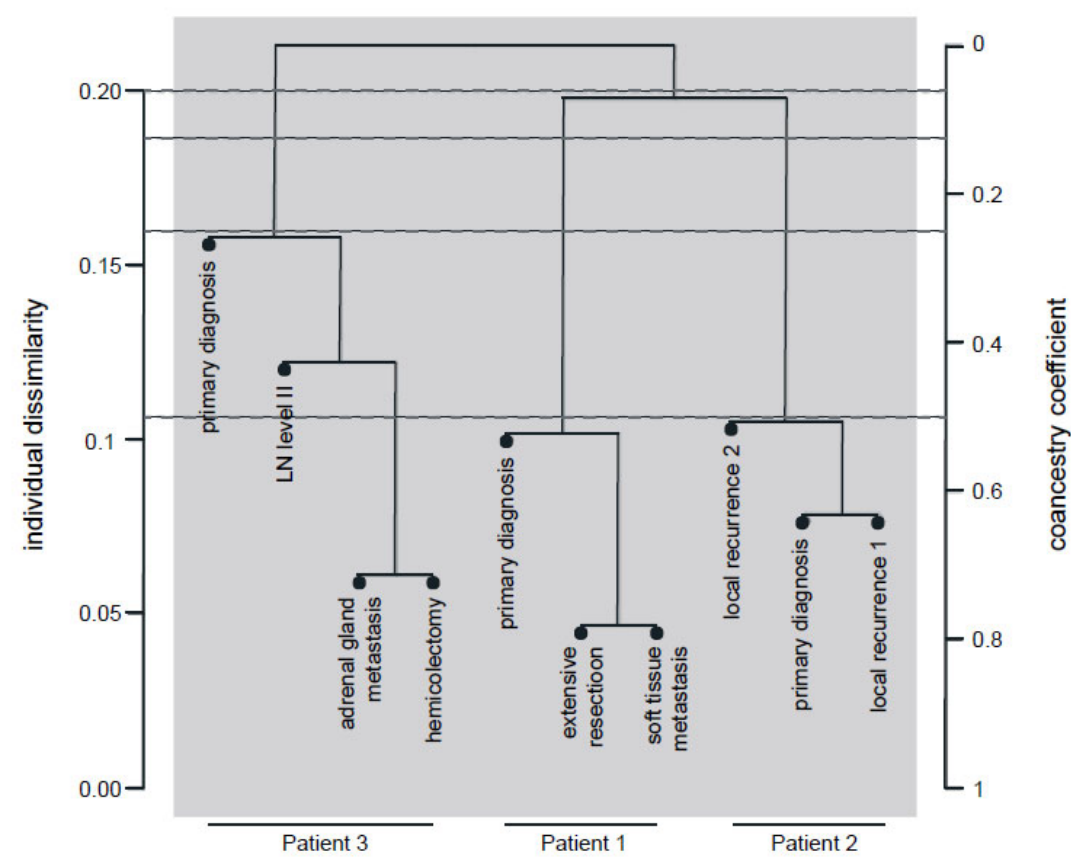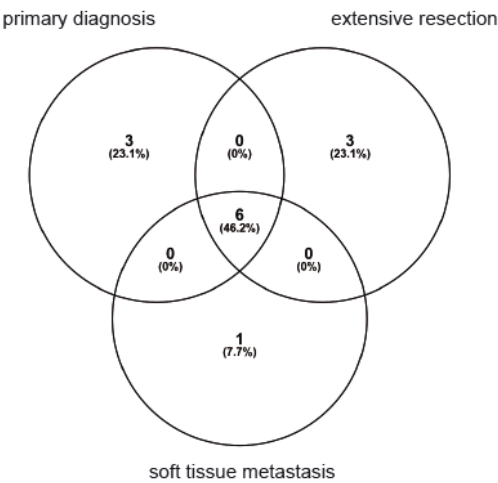**Supplementary Appendix**

Table of content
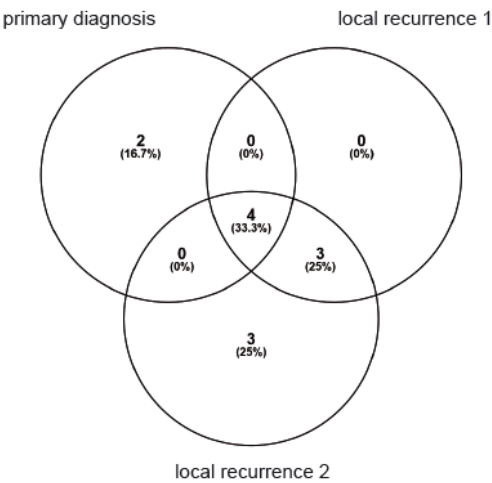
Figure S1: Individual dissimilarity and co-ancestry coefficient of all resected tumors from all patients.

Figure S2

A

primary diagnosis   extensive resection

3 (23.1%)   0 (0%)   3 (23.1%)

6 (46.2%)

0 (0%)   0 (0%)

1 (7.7%)

soft tissue metastasis

B

primary diagnosis   local recurrence 1

2 (16.7%)   0 (0%)   0 (0%)

4 (33.3%)

0 (0%)   3 (25%)

3 (25%)

local recurrence 2

C

LN level II   hemicolectomy

1 (3.7%)   2 (7.4%)

0 (0%)   0 (0%)   1 (3.7%)

1 (3.7%)   1 (3.7%)   0 (0%)   3 (11.1%)

13 (48.1%)

0 (0%)   3 (11.1%)

0 (0%)   2 (7.4%)

0 (0%)

primary diagnosis   adrenal gland metastasis

D

patient 2 local recurrence 1   patient 2 local recurrence 2

0 (0%)   3 (7.9%)

0 (0%)   6 (15.8%)   0 (0%)

7 (18.4%)   0 (0%)   1 (2.6%)   21 (55.3%)

0 (0%)

0 (0%)   0 (0%)   0 (0%)

0 (0%)   0 (0%)

patient 1 soft tissue metastasis   0 (0%)   patient 3 adrenal gland metastasis
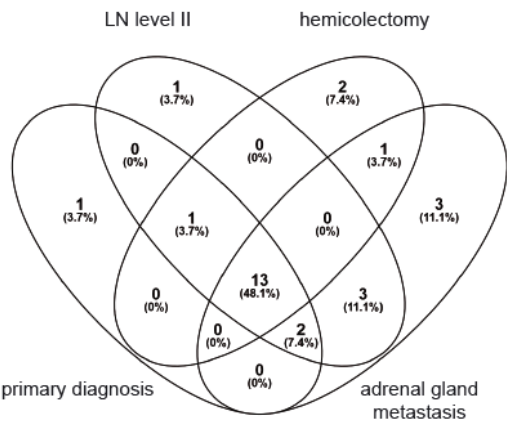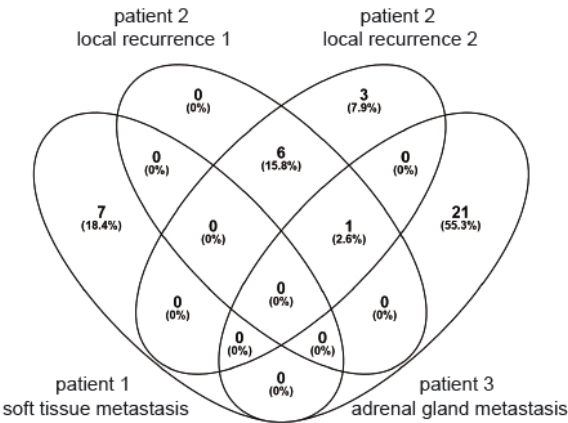
Figure S2: Overlap of mutations of the different tumor manifestations within each patient and of the *NRAS* mutant tumors. A) patient 1, B) patient 2, C) patient 3, D) overlap of mutations of *NRAS* mutant tumors of the three patients. LN: lymph node
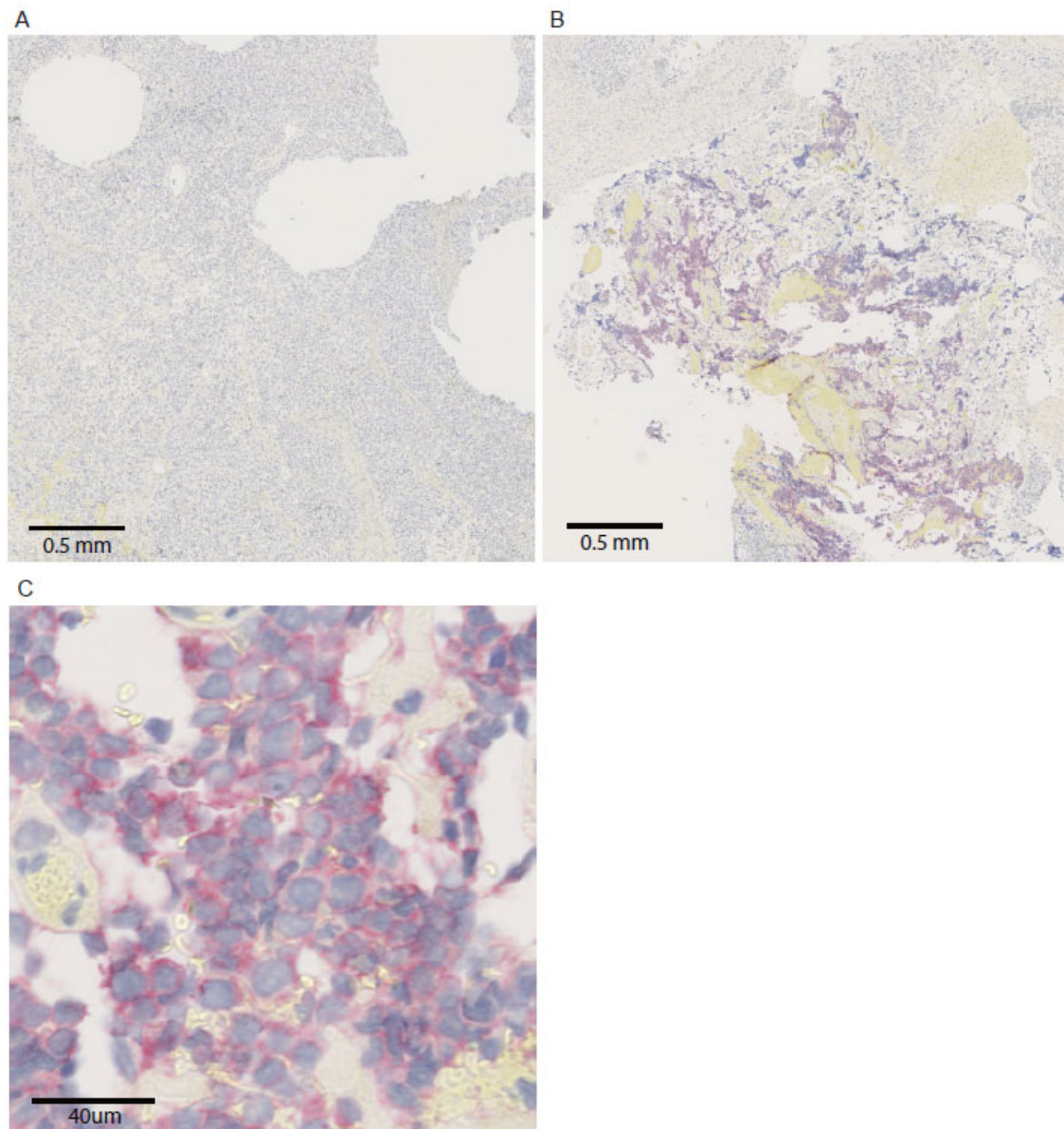
Figure S3

Figure S3: NRAS Q61R staining of the primary tumor of patient 1. A) Overview of the *KIT* mutant region, B) overview of the *NRAS* mutant region, C) higher magnification of the *NRAS* mutant region. Scale bar: 40um

Figure S4

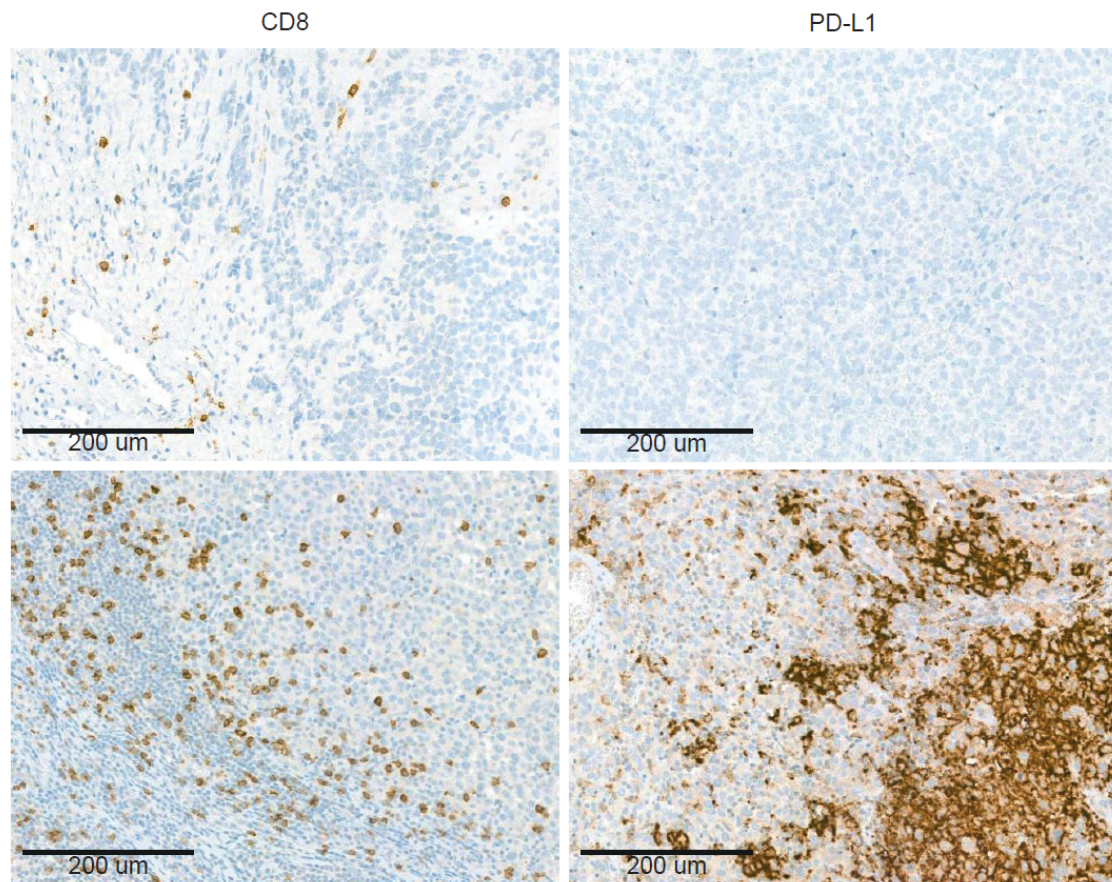CD8   PD-L1

Figure S4: Examples for CD8 and PD-L1 staining. Examples for single CD8+ cells infiltrating within the tumor with moderate accumulation at the tumor margin (upper left), negative PD-L1 staining (upper right), moderate infiltration of CD8+ cells within the tumor and high accumulation at the tumor margin (lower left), and strong PD-L1 staining (lower right).

Table S1: List of genes included in the MelArray NGS panel.

ABCB5	CCND3	ETV6	KMT2C	PIK3C2A	PTPRJ	TERF2IP
ACD	CDC42	EZH2	KMT2D	PIK3C3	PTPRK	TERT
ACVR1C	CDK4	FAM58A	KNSTRN	PIK3CA	RAC1	TNRC6B
AKAP9	CDK6	FANCA	KRAS	PIK3CB	RAD51B	TP53
AKT1	CDKN1A	FBXW7	MAP2K1	PIK3R1	RAF1	TRRAP
AKT2	CDKN1B	FGFR1	MAP2K2	PIK3R4	RASA1	TSC1
AKT3	CDKN2A	FGFR2	MAP2K4	PIKFYVE	RASA2	TSC2
ALK	CDKN2C	FGFR3	MAP3K1	PKD2	RASA3	TUSC3
ANP32C	CHD8	FGFR4	MAP3K2	PLA2G6	RB1	TYR
APC	CTNNB1	FYN	MAP3K5	PLCB1	RET	TYRP1
ARID1A	CXCL1	GNA11	MAP3K8	PLCE1	RICTOR	
ARID1B	CYP1B1	GNAI2	MAP3K9	PLEKHG4	ROS1	
ARID2	CYP7B1	GNAQ	MAPK1	PMEL	RQCD1	
ARID4B	DCT	GNAS	MAPK3	PMS2	SETD2	
ARID5A	DCUN1D3	HERC2	MC1R	POLQ	SF3B1	
ASIP	DDR2	HLA-A	MET	POT1	SHOC2	
ASPM	DDX3X	HLA-B	MITF	PPARG	SLC1A4	
ATM	DLG1	HLA-C	MLH1	PPP2R2A	SLC45A2	
AURKA	DNMT1	HRAS	MLH3	PPP2R2B	SMARCA4	
AURKB	DNMT3A	IDH1	MTOR	PPP2R5C	SMO	
BAP1	DNMT3B	IGF2R	MYCN	PPP3CA	SOS1	
BCL2	DPP3	IQGAP1	NF1	PPP6C	SOS2	
BCL2L12	DYNC1I1	ITGA5	NFKBIE	PRAME	SPRED1	
BCLAF1	E2F1	JAK1	NOTCH2	PRKAR1A	SPRED2	
BRAF	EGFR	JAK2	NRAS	PRKCD	SPRY4	
BRCA1	EIF1AX	JARID2	NTRK1	PROS1	SRC	
BRCA2	EIF4A1	KDR	OCA2	PTCH1	STK11	
CBL	EP300	KIT	PARP1	PTEN	TAOK1	
CCND1	ERBB2	KMT2A	PCDHGA1	PTPN11	TAOK2	
CCND2	ERBB3	KMT2B	PDGFRA	PTPRF	TERF2	

Table S2: Mutational profile of all tumors of patient 1 acquired by MelArray NGS panel.

patient 1

primary diagnosis		
gene	**mutation**	**frequency**
ACVR1C	p.Asn150His	40.1%
ARID5A	p.Pro375Arg	40.5%
ASPM	p.Tyr3353His	50.5%
ASPM	p.Gly1099AlafsTer15	52.8%
KMT2B	p.Met390Thr	40.3%
KMT2C	p.Gly3843Ala	47.4%
KRAS	p.Gly12Arg	78.0%
PKD2	p.Ser804Asn	51.7%
TERT	p.His412Tyr	35.1%
extensive resection		
gene	**mutation**	**frequency**
ARID5A	p.Pro375Arg	55.4%
ASPM	p.Tyr3353His	64.0%
ASPM	p.Gly1099AlafsTer15	60.8%
IDH1	p.Arg132Cys	48.5%
KIT	p.Asp816His	56.7%
KMT2B	p.Met390Thr	49.9%
NF1	p.Gln1315Ter	42.0%
PKD2	p.Ser804Asn	51.9%
TERT	p.His412Tyr	49.6%
sof tissue metastasis		
gene	**mutation**	**frequency**
ARID5A	p.Pro375Arg	21.6%
ASPM	p.Tyr3353His	36.2%
ASPM	p.Gly1099AlafsTer15	37.3%
KMT2B	p.Met390Thr	49.8%
NRAS	p.Gln61Arg	91.8%
PKD2	p.Ser804Asn	47.2%
TERT	p.His412Tyr	36.3%

Table S3: Mutational profile of all tumors of patient 2 acquired by MelArray NGS panel.

patient 2

primary diagnosis		
gene	**mutation**	**frequency**
AKAP9	p.Met3743Ile	63.7%
ALK	p.Glu1400Asp	61.2%
FGFR2	p.Met671Thr	90.0%
KMT2A	p.Arg2191Gln	59.1%
KRAS	p.Gly12Ala	66.7%
PLEKHG4	p.Glu756Gly	35.3%
local recurrence 1		
gene	**mutation**	**frequency**
AKAP9	p.Met3743Ile	50.8%
ALK	p.Glu1400Asp	51.4%
HERC2	p.Gly4582Glu	86.1%
KMT2A	p.Arg2191Gln	46.4%
NRAS	p.Gln61Lys	47.7%
PLEKHG4	p.Glu756Gly	56.4%
SMARCA4	p.Trp1346Cys	67.8%
local recurrence 2		
gene	**mutation**	**frequency**
AKAP9	p.Met3743Ile	43.7%
ALK	p.Glu1400Asp	49.4%
ARID1B	p.Ala457GlyfsTer49	23.7%
HERC2	p.Gly4582Glu	29.6%
KMT2A	p.Arg2191Gln	45.8%
NRAS	p.Gln61Lys	16.7%
PLCB1	p.Pro813GlnfsTer5	13.0%
PLEKHG4	p.Glu756Gly	46.2%
PTPRK	p.Arg1039Ser	6.8%
SMARCA4	p.Trp1346Cys	53.1%

Table S4: Mutational profile of all tumors of patient 3 acquired by MelArray NGS panel.

patient 3

primary diagnosis		
gene	**mutation**	**frequency**
BRCA2	p.Glu1120Lys	33.1%
GNAS	p.Asp466_Ala467insSerGlyAlaAlaArgAspAlaProAlaAspProAsp	53.5%
JAK2	p.Leu579Phe	30.3%
KMT2A	p.Pro58ArgfsTer92	5.2%
KMT2C	p.Pro3367Ser	15.0%
MAP3K9	p.Ser909Phe	94.0%
MITF	p.Leu400ProfsTer24	74.3%
PARP1	p.His476Tyr	14.0%
PIK3C2A	p.Glu1028Lys	28.1%
PIK3C3	p.Ser128Leu	44.8%
PIKFYVE	p.Glu942Lys	22.9%
PLCE1	p.Asp1102Asn	29.2%
PROS1	p.Arg316Cys	47.4%
PTPRK	p.Glu1373Lys	46.1%
SLC1A4	p.Val289Met	74.1%
SOS1	p.Arg310Cys	23.4%
SOS2	p.Val680Ile	30.1%
LN Level III		
gene	**mutation**	**frequency**
BCL2	p.Leu185Pro	26.5%
BRCA2	p.Glu1120Lys	18.6%
GNAQ	p.Met1?	6.0%
GNAS	p.Asp466_Ala467insSerGlyAlaAlaArgAspAlaProAlaAspProAsp	55.7%
HERC2	p.Pro339Ser	13.6%
JAK2	p.Leu579Phe	19.1%
KMT2C	p.Pro3367Ser	25.5%
KMT2D	p.Trp5264Cys	23.7%
MAP3K9	p.Ser909Phe	63.1%
MITF	p.Leu400ProfsTer24	72.6%
PARP1	p.His476Tyr	11.8%
PIK3C2A	p.Glu1028Lys	22.0%
PIK3C3	p.Ser128Leu	26.0%
PIKFYVE	p.Glu942Lys	22.2%
PLCE1	p.Asp1102Asn	22.2%
PROS1	p.Arg316Cys	34.6%
PTPRK	p.Glu1373Lys	25.0%
SLC1A4	p.Val289Met	59.1%
SOS1	p.Arg310Cys	23.0%
SOS2	p.Val680Ile	20.6%
Hemicolectomy		
gene	**mutation**	**frequency**
BRCA2	p.Glu1120Lys	34.7%
JAK2	p.Leu579Phe	30.0%
KMT2C	p.Pro3367Ser	21.1%
MAP3K9	p.Ser909Phe	87.7%
MITF	p.Leu400ProfsTer24	82.7%
PARP1	p.His476Tyr	19.3%

PIK3C2A	p.Glu1028Lys	32.5%
PIK3C3	p.Ser128Leu	37.4%
PIK3CA	p.Cys420Arg	20.2%
PIKFYVE	p.Glu942Lys	23.2%
PLCE1	p.Asp1102Asn	32.9%
PROS1	p.Arg316Cys	43.6%
PTPRJ	c.2153-2A>C	33.5%
PTPRK	p.Glu1373Lys	32.5%
ROS1	c.5249-8C>T	80.5%
SOS1	p.Arg310Cys	26.0%
SOS2	p.Val680Ile	37.2%
Adrenal gland metastasis		
gene	**mutation**	**frequency**
BCL2	p.Leu185Pro	37.8%
BCLAF1	p.Arg47Cys	6.9%
BCLAF1	c.-10-5_-10-4insCTTC	8.4%
BRCA2	p.Glu1120Lys	22.3%
GNAQ	p.Met1?	5.3%
GNAS	p.Asp466_Ala467insSerGlyAlaAlaArgAspAlaProAlaAspProAsp	33.2%
KMT2C	p.Pro3367Ser	20.1%
KMT2D	p.Trp5264Cys	25.7%
MAP3K9	p.Ser909Phe	83.3%
MITF	p.Leu400ProfsTer24	94.6%
NRAS	p.Gln61Lys	12.3%
PARP1	p.His476Tyr	13.5%
PIK3C2A	p.Glu1028Lys	52.9%
PIK3C3	p.Ser128Leu	35.1%
PIKFYVE	p.Glu942Lys	20.8%
PLCE1	p.Asp1102Asn	25.0%
PROS1	p.Arg316Cys	43.0%
PTPRK	p.Glu1373Lys	42.5%
ROS1	c.5249-8C>T	78.9%
SLC1A4	p.Val289Met	69.4%
SOS1	p.Arg310Cys	20.8%
SOS2	p.Val680Ile	21.9%

Table S5: Mutational analysis of sinonasal melanoma before and after immunotherapy

	Before RT	After RT
RT-pat. 1	wild type for *KRAS*, *NRAS*, *KIT* *PTEN* p.V166Sfs*14	wild type for *KRAS*, *NRAS*, *KIT* *PTEN* p.V166Sfs*14, *BRCA2* p.T2125Nfs*4
RT-pat. 2	wild type for *KRAS*, *NRAS*, *KIT* *TP53* p.R273C	wild type for *KRAS*, *NRAS*, *KIT* *TP53* p.R273C
RT-pat. 3	wild type for *BRAF*, *NRAS*, *KIT*	wild type for *BRAF*, *NRAS*, *KIT*

RT = radio therapy

Table S6: Distribution of CD8+ cells and PD-L1 status in all assessed tumors.

	sample	mutation	CD8	PD-L1
patient 1	primary diagnosis	*KRAS* p.G12R	central negative, peripherally moderate	TC0, IC1
	extensive resection	*KIT* p.D916H	central negative, peripherally single positive cells	TC0, IC0
	sof tissue metastasis	*NRAS* p.Q61R	central moderate, peripherally moderate	TC0, IC1
patient 2	primary diagnosis	*KRAS* p.G12A	central single pos cells, peripheral modeate	TC0, IC0
	local recurrence 1	*NRAS* p.Q61K	central moderate, peripheral high	TC0, IC1
patient 3	primary diagnosis	WT	central single pos cells, peripheral modeate	TC0, IC0
	LN Level III	WT	central moderate, peripheral high	TC2, IC2
	Adrenal gland metastasis	*NRAS* p.Q61K	central single pos cells, peripheral modeate	TC2, IC3

Table S7: Mutational burden of all samples as calculated by MelArray

		number of mutations	mutations / Mb
patient 1	primary diagnosis	9	13.8
	extensive resection	9	13.8
	sof tissue metastasis	7	10.8
patient 2	primary diagnosis	6	9.2
	local recurrence 1	7	10.8
	local recurrence 2	10	15.4
patient 3	primary diagnosis	17	26.2
	LN Level III	20	30.8
	Hemicolectomy	15	23.1
	Adrenal gland metastasis	20	30.8