Supplementary Table S1. Real-world cohort of fresh tissue biopsies belonging to 36 melanoma patients.

BRAF V600+ Patients		Total N=19	R	NR
SEX		F	4	6*
		M	4	5
PRE-THERAPY BIOPSY			1	9*
POST-THERAPY BIOPSY			7	2
TUMOUR ONSET MEDIAN			55.5y	54.1y
THERAPY	BRAF+MEKi		6	7
	Anti-PD-1		2	1
	Adjuvant with BRAF+MEKi		0	3*
BRAF V600- Patients		Total N=17	R	NR
SEX		F	3	3
		M	6	5
PRE-THERAPY BIOPSY			4	5
POST-THERAPY BIOPSY			5	3
TUMOUR ONSET MEDIAN			69.7y	62.7y

	Anti-PD-1	6	3
	Anti-CTLA-4	1	0
THERAPY	Imatinib	0	1
	Adjuvant with Anti-PD-1	2	3
	Ipilimumab/Adjuvant with Anti-PD-1	0	1

*Abbreviations: F: Female; M: Male; y: years; R: Responder; NR: Non-Responder; *: 1 FFPE biopsy analysed.*

Supplementary Table S2. Association between genetic layout and response to therapy.

VARIABLE	SAMPLES	RESPONSE TO THERAPY	MEDIAN	IQR	Test statistic	p-value
TMB	ALL	R	22.89	10.61-44.28	W = 197	p= 0.271
		NR	16.04	5.3-39		
	BRAF+	R	25.76	13.49-51.84	W = 46	p= 0.904
		NR	34.77	7.53-43.97		
	BRAF-	R	21.91	10.51-44.28	W = 51	p=0.167
		NR	10.4	4.22-24.95		
N mutations in melanoma driver genes	ALL	R	2	1-3	W = 211	p= 0.113
		NR	3	2-5		
	BRAF+	R	1.5	0.75-3.25	W = 26.5	p= 0.152
		NR	3	1.5-5		
	BRAF-	R	2	1-3	W = 26	p= 0.348
		NR	3	2-3.5		
N CNVs in melanoma driver genes	ALL	R	3	1-8	W = 152.5	p= 0.786
		NR	4	0.5-11		
	BRAF+	R	3.5	1.75-7.5	W = 40	p= 0.769
		NR	9	0-11.5		
	BRAF-	R	3	1-8	W = 35	p= 0.961
		NR	3	1.75-5.5		
N DNA Damage Repair genes with LOH	ALL	R	0	0-21	W = 217	p= 0.062
		NR	12	0-35		

			N	IQR		
	BRAF+	R	0	0-6.75	W = 57	p= 0.264
		NR	12	0-21.5		
	BRAF-	R	0	0-21	W = 52	p= 0.115
		NR	20	8.25-47		
COSMIC Signatures	ALL	R	-	-	-	p= 0.754
		NR	-	-		
	BRAF+	R	-	-	-	p= 0.699
		NR	-	-		
	BRAF-	R	-	-	-	p= 0.174
		NR	-	-		
TERT promoter mutations (Yes/No)	ALL	R	-	-	OR = 0.23 (CI = 0.02 - 1.58)	p= 0.118
		NR	-	-		
	BRAF+	R	-	-	OR = 0 (CI = 0 - 2.31)	p= 0.234
		NR	-	-		
	BRAF-	R	-	-	OR = 0.36 (CI = 0.02 - 5.11)	p= 0.580
		NR	-	-		

Abbreviations: N = number of samples; R= responders; NR= non-responders; BRAF+= BRAF-mutated samples; BRAF-= BRAF wild-type samples; W= Wilcoxon rank sum test statistic; OR = odds ratio (in this case, odds that the outcome occurs in R group compared to the odds of the outcome occurring in NR); IQR = inter-quartile range; CI = 95% confidence interval; TMB= tumor mutation burden; LOH= loss of heterozygosity; CNV= copy number variation.

Supplementary Table S3. Loss Of Heterozygosity (LOH) in DNA Damage Repair (DDR) genes for our 36 melanomas patient's cohort.

Gene	Sample ID	*BRAF* V600 status	R
AEN	#47	-	n
ALKBH1	#56	+	n
ALKBH3	#56	+	n
	#4	-	y
	#54	-	n
APEX1	#56	+	n
APEX2	#39	+	y
	#19	+	n
	#43	+	n
	#56	+	n
	#1	+	n
	#8	+	n
	#10	+	n
	#50	+	n
	#4	-	y
	#59	-	y
	#32	-	y
	#45	-	n
	#55	-	n
	#63	-	n
	#47	-	n
	#57	-	n
APLF	#47	-	n
APTX	#30	+	y
	#56	+	n
	#10	+	n

	#59	-	y
	#32	-	y
	#45	-	n
	#54	-	n
	#47	-	n
ASCC3	#39	+	y
	#10	+	n
	#45	-	n
	#63	-	n
ATM	#39	+	y
	#56	+	n
	#4	-	y
	#54	-	n
ATR	#56	+	n
ATRIP	#56	+	n
ATRX	#39	+	y
	#19	+	n
	#43	+	n
	#56	+	n
	#1	+	n
	#8	+	n
	#10	+	n
	#50	+	n
	#4	-	y
	#59	-	y
	#32	-	y
	#45	-	n
	#55	-	n
	#63	-	n
	#47	-	n
	#57	-	n

BABAM1	#59	-	y
BARD1	#47	-	n
BCAS2	#56	+	n
	#47	-	n
BLM	#63	-	n
	#47	-	n
BRCA1	#43	+	n
	#1	+	n
	#8	+	n
	#4	-	y
	#45	-	n
	#54	-	n
BRCA2	#43	+	n
	#8	+	n
	#10	+	n
BRCC3	#39	+	y
	#19	+	n
	#43	+	n
	#56	+	n
	#1	+	n
	#8	+	n
	#10	+	n
	#50	+	n
	#4	-	y
	#59	-	y
	#32	-	y
	#45	-	n
	#55	-	n
	#54	-	n
	#63	-	n
	#47	-	n

	#57	-	n
CCNH	#56	+	n
	#47	-	n
CDC25A	#56	+	n
CDC25C	#47	-	n
CETN2	#39	+	y
	#19	+	n
	#43	+	n
	#56	+	n
	#1	+	n
	#8	+	n
	#10	+	n
	#50	+	n
	#4	-	y
	#59	-	y
	#32	-	y
	#45	-	n
	#55	-	n
	#54	-	n
	#63	-	n
	#47	-	n
	#57	-	n
CHAF1A	#59	-	y
	#54	-	n
CHEK1	#39	+	y
	#56	+	n
	#4	-	y
	#59	-	y
	#45	-	n
	#63	-	n
CHEK2	#47	-	n

CUL3	#59	-	y
	#47	-	n
CUL5	#39	+	y
	#56	+	n
	#4	-	y
	#54	-	n
DCLRE1A	#39	+	y
	#30	+	y
	#19	+	n
	#56	+	n
	#10	+	n
	#45	-	n
	#63	-	n
DCLRE1B	#56	+	n
	#47	-	n
DCLRE1C	#30	+	y
	#19	+	n
	#56	+	n
	#10	+	n
	#45	-	n
	#63	-	n
DDB1	#19	+	n
	#56	+	n
	#4	-	y
DDB2	#56	+	n
	#4	-	y
DMC1	#50	+	n
	#54	-	n
	#47	-	n
DNA2	#39	+	y
	#30	+	y

	#19	+	n
	#56	+	n
	#10	+	n
	#59	-	y
	#45	-	n
DNTT	#39	+	y
	#30	+	y
	#19	+	n
	#56	+	n
	#10	+	n
	#45	-	n
	#63	-	n
DUT	#39	+	y
	#63	-	n
	#47	-	n
EME1	#4	-	y
EME2	#47	-	n
ENDOV	#10	+	n
ERCC2	#59	-	y
ERCC3	#47	-	n
ERCC4	#59	-	y
	#47	-	n
ERCC6	#39	+	y
	#30	+	y
	#56	+	n
	#10	+	n
	#45	-	n
	#63	-	n
ERCC8	#57	-	n
EXO1	#39	+	y
EXO5	#47	-	n

FAAP20	#10	+	n
	#4	-	y
	#47	-	n
FANCA	#39	+	y
	#56	+	n
	#59	-	y
	#45	-	n
	#63	-	n
	#47	-	n
FANCB	#39	+	y
	#19	+	n
	#43	+	n
	#56	+	n
	#1	+	n
	#8	+	n
	#10	+	n
	#50	+	n
	#4	-	y
	#59	-	y
	#32	-	y
	#45	-	n
	#55	-	n
	#54	-	n
	#63	-	n
	#47	-	n
	#57	-	n
FANCC	#30	+	y
	#56	+	n
	#10	+	n
	#32	-	y
	#45	-	n

	#47	-	n
FANCD2	#39	+	y
	#56	+	n
FANCE	#56	+	n
FANCF	#56	+	n
	#4	-	y
	#54	-	n
	#63	-	n
FANCG	#30	+	y
	#56	+	n
	#10	+	n
	#32	-	y
	#45	-	n
	#54	-	n
	#47	-	n
FANCI	#47	-	n
FANCL	#56	+	n
	#4	-	y
	#47	-	n
FANCM	#56	+	n
	#59	-	y
FEN1	#56	+	n
	#4	-	y
GADD45A	#47	-	n
GADD45G	#30	+	y
	#56	+	n
	#10	+	n
	#59	-	y
	#32	-	y
	#45	-	n
	#47	-	n

gen-01	#47	-	n
GTF2H1	#56	+	n
	#4	-	y
	#54	-	n
GTF2H3	#4	-	y
	#45	-	n
GTF2H5	#39	+	y
	#56	+	n
	#59	-	y
	#32	-	y
	#45	-	n
	#63	-	n
H2AFX	#39	+	y
	#56	+	n
	#4	-	y
	#59	-	y
	#54	-	n
	#63	-	n
HELQ	#56	+	n
	#63	-	n
HERC2	#39	+	y
	#63	-	n
	#47	-	n
HES1	#56	+	n
HFM1	#47	-	n
HLTF	#56	+	n
HMGB2	#56	+	n
	#59	-	y
	#63	-	n
HUS1	#19	+	n
	#54	-	n

IDH1	#47	-	n
INO80	#39	+	y
	#19	+	n
	#63	-	n
	#47	-	n
KAT5	#56	+	n
	#4	-	y
	#54	-	n
LIG4	#30	+	y
	#56	+	n
	#57	-	n
MAD2L2	#10	+	n
	#4	-	y
	#47	-	n
MBD4	#56	+	n
MGMT	#39	+	y
	#30	+	y
	#19	+	n
	#56	+	n
	#10	+	n
	#45	-	n
	#63	-	n
MLH1	#56	+	n
MLH3	#56	+	n
MMS19	#39	+	y
	#30	+	y
	#19	+	n
	#56	+	n
	#10	+	n
	#63	-	n
MNAT1	#56	+	n

MORF4L1	#47	-	n
MPG	#47	-	n
MRPL40	#47	-	n
MSH2	#10	+	n
	#59	-	y
	#47	-	n
MSH6	#47	-	n
MUS81	#56	+	n
	#4	-	y
	#54	-	n
MUTYH	#47	-	n
NBN	#4	-	y
	#54	-	n
NEIL1	#59	-	y
	#47	-	n
NEIL2	#56	+	n
	#4	-	y
NEIL3	#56	+	n
	#50	+	n
	#59	-	y
	#63	-	n
NFATC2IP	#47	-	n
NHEJ1	#47	-	n
NSMCE1	#59	-	y
	#47	-	n
NSMCE2	#47	-	n
NSMCE4A	#39	+	y
	#30	+	y
	#19	+	n
	#56	+	n
	#10	+	n

	#45	-	n
	#63	-	n
NTHL1	#47	-	n
NUDT1	#59	-	y
NUDT18	#56	+	n
	#4	-	y
OGG1	#39	+	y
	#56	+	n
PALB2	#47	-	n
PARG	#39	+	y
	#30	+	y
	#56	+	n
	#10	+	n
	#63	-	n
PARP1	#39	+	y
PARP2	#56	+	n
PARP3	#56	+	n
	#54	-	n
PARP4	#10	+	n
PAXIP1	#30	+	y
	#56	+	n
PER1	#19	+	n
	#45	-	n
PLK3	#47	-	n
PLRG1	#56	+	n
	#59	-	y
	#63	-	n
PMS1	#47	-	n
PMS2	#45	-	n
PNKP	#43	+	n
	#59	-	y

	#39	+	y
	#19	+	n
	#43	+	n
	#56	+	n
	#1	+	n
	#8	+	n
	#10	+	n
	#50	+	n
POLA1	#4	-	y
	#59	-	y
	#32	-	y
	#45	-	n
	#55	-	n
	#54	-	n
	#63	-	n
	#47	-	n
	#57	-	n
POLB	#56	+	n
	#4	-	y
POLD3	#56	+	n
	#4	-	y
POLD4	#56	+	n
	#4	-	y
	#59	-	y
	#54	-	n
POLE	#8	+	n
	#4	-	y
	#59	-	y
POLE2	#56	+	n
	#59	-	y
POLE3	#30	+	y

	#56	+	n
	#10	+	n
	#32	-	y
	#45	-	n
	#47	-	n
POLE4	#47	-	n
POLG	#47	-	n
POLI	#54	-	n
POLL	#39	+	y
	#30	+	y
	#19	+	n
	#10	+	n
	#45	-	n
	#63	-	n
POLN	#43	+	n
	#56	+	n
	#59	-	y
	#45	-	n
	#63	-	n
POLQ	#56	+	n
	#50	+	n
PPP4C	#47	-	n
PPP4R1	#43	+	n
	#59	-	y
PPP4R2	#56	+	n
PRKDC	#4	-	y
	#63	-	n
PRPF19	#56	+	n
	#4	-	y
PTEN	#39	+	y
	#30	+	y

	#56	+	n
	#10	+	n
	#45	-	n
	#63	-	n
RAD18	#39	+	y
	#56	+	n
RAD23B	#30	+	y
	#56	+	n
	#10	+	n
	#32	-	y
	#45	-	n
	#47	-	n
RAD50	#47	-	n
RAD51	#39	+	y
	#19	+	n
	#63	-	n
	#47	-	n
RAD51B	#56	+	n
	#56	+	n
	#45	-	n
RAD52	#59	-	y
	#63	-	n
RAD54B	#4	-	y
RAD54L	#47	-	n
RAD9A	#56	+	n
	#4	-	y
	#59	-	y
	#54	-	n
RBBP8	#59	-	y
RBX1	#47	-	n
RECQL4	#55	-	n

	#47	-	n
RECQL5	#10	+	n
REV1	#47	-	n
REV3L	#39	+	y
	#10	+	n
	#59	-	y
	#45	-	n
	#63	-	n
RFC1	#56	+	n
	#63	-	n
RFC2	#30	+	y
	#56	+	n
RFC3	#56	+	n
RFC4	#56	+	n
RIF1	#39	+	y
	#55	-	n
	#54	-	n
	#47	-	n
RMI1	#30	+	y
	#56	+	n
	#10	+	n
	#32	-	y
	#45	-	n
	#47	-	n
RMI2	#47	-	n
RNF168	#56	+	n
RNF169	#56	+	n
	#4	-	y
RNF4	#56	+	n
	#1	+	n
	#63	-	n

RNMT	#43	+	n
	#59	-	y
RPA1	#19	+	n
	#45	-	n
RPA2	#10	+	n
	#47	-	n
RPA4	#39	+	y
	#19	+	n
	#43	+	n
	#56	+	n
	#1	+	n
	#8	+	n
	#10	+	n
	#50	+	n
	#4	-	y
	#59	-	y
	#32	-	y
	#45	-	n
	#55	-	n
	#63	-	n
	#47	-	n
	#57	-	n
RRM1	#56	+	n
	#4	-	y
	#45	-	n
RRM2	#47	-	n
RRM2B	#59	-	y
	#47	-	n
SETMAR	#39	+	y
	#30	+	y
	#56	+	n

	#39	+	y
	#56	+	n
SHPRH	#32	-	y
	#45	-	n
	#63	-	n
	#45	-	n
SLX1A	#45	-	n
	#47	-	n
SLX4	#47	-	n
SMARCA4	#54	-	n
	#56	+	n
SMARCAD1	#63	-	n
	#47	-	n
SMARCC1	#56	+	n
	#30	+	y
	#56	+	n
	#10	+	n
SMC5	#59	-	y
	#32	-	y
	#45	-	n
	#47	-	n
SMC6	#47	-	n
SOX4	#56	+	n
SPRTN	#39	+	y
	#30	+	y
	#56	+	n
	#10	+	n
SWI5	#32	-	y
	#45	-	n
	#47	-	n
SWSAP1	#54	-	n

Gene	Sample	+/-	y/n
TCEA1	#4	-	y
	#59	-	y
TDP1	#56	+	n
TDP2	#56	+	n
TELO2	#47	-	n
TOP3A	#19	+	n
TOP3B	#47	-	n
TOPBP1	#56	+	n
TP53	#19	+	n
	#45	-	n
TP53BP1	#39	+	y
	#63	-	n
	#63	-	n
	#47	-	n
TREX1	#56	+	n
TREX2	#39	+	y
	#19	+	n
	#43	+	n
	#56	+	n
	#1	+	n
	#8	+	n
	#10	+	n
	#50	+	n
	#4	-	y
	#59	-	y
	#32	-	y
	#45	-	n
	#55	-	n
	#54	-	n
	#63	-	n
	#47	-	n

	#57	-	n
TTK	#39	+	y
	#10	+	n
	#63	-	n
TYMS	#43	+	n
	#59	-	y
	#45	-	n
UBE2A	#39	+	y
	#19	+	n
	#43	+	n
	#56	+	n
	#1	+	n
	#8	+	n
	#10	+	n
	#50	+	n
	#4	-	y
	#59	-	y
	#32	-	y
	#45	-	n
	#55	-	n
	#63	-	n
	#47	-	n
	#57	-	n
UBE2B	#47	-	n
UBE2T	#39	+	y
UBE2V2	#4	-	y
	#63	-	n
UIMC1	#47	-	n
USP1	#47	-	n
UVSSA	#43	+	n
	#56	+	n

	#63	-	n
WDR48	#56	+	n
WEE1	#56	+	n
	#4	-	y
	#54	-	n
WRN	#56	+	n
	#4	-	y
XAB2	#54	-	n
XPA	#30	+	y
	#56	+	n
	#10	+	n
	#32	-	y
	#45	-	n
	#47	-	n
XPC	#56	+	n
XRCC2	#30	+	y
	#56	+	n
	#59	-	y
XRCC3	#56	+	n
XRCC5	#47	-	n
XRCC6	#47	-	n
YWHAG	#30	+	y
ZSWIM7	#19	+	n
	#45	-	n

Abbreviations: R: Response; y: yes; n: no

Supplementary Table S4. Mutational Signature.

Mutational Signature for our 36 melanomas patient's cohort and comparison between three different tools (DeconstructSigs, SigMa, and SigProfiler v3.2).

Sample ID	*BRAF* V600 Status	deconstructSig	SigMa	ssSigProfiler
#1	+	Signature_3	Signature_3_hc	SBS3
#2	+	Signature_3	Signature_3_hc	SBS3
#3	+	Signature_3	Signature_3_hc	SBS3
#8	+	Signature_3	Signature_3_hc	SBS3
#10	+	Signature_3	Signature_3_hc	SBS3
#14	+	Signature_3	Signature_3_hc	SBS3
#17	+	Signature_clock-like	Signature_clock	SBS5
#19	+	Signature_UV	Signature_UV	SBS7
#26	+	Signature_clock-like	Signature_clock	SBS5
#30	+	Signature_UV	Signature_UV	SBS7
#37	+	Signature_clock-like	Signature_clock	SBS5
#39	+	Signature_UV	Signature_UV	SBS7
#40	+	Signature_UV	Signature_UV	SBS7
#42	+	Signature_clock-like	Signature_3_hc	SBS3
#43	+	Signature_clock-like	Signature_msi	SBS1
#50	+	Signature_clock-like	Signature_clock	SBS5
#56	+	Signature_clock-like	Signature_clock	SBS5

#60	+	Signature_UV	Signature_UV	SBS7
#62	+	Signature_UV	Signature_UV	SBS7
#4	-	Signature_UV	Signature_UV	SBS7
#6	-	Signature_3	Signature_3_hc	SBS3
#7	-	Signature_UV	Signature_UV	SBS7
#18	-	Signature_UV	Signature_UV	SBS7
#20	-	Signature_UV	Signature_UV	SBS7
#21	-	Signature_3	Signature_3_hc	SBS3
#32	-	Signature_UV	Signature_UV	SBS7
#34	-	Signature_3	Signature_3_hc	SBS3
#38	-	Signature_UV	Signature_UV	SBS7
#45	-	Signature_UV	Signature_UV	SBS7
#46	-	Signature_3	Signature_3_hc	SBS3
#47	-	Signature_clock-like	Signature_clock	SBS5
#54	-	Signature_clock-like	Signature_clock	SBS5
#55	-	Signature_clock-like	Signature_UV	SBS7
#57	-	Signature_UV	Signature_UV	SBS7
#59	-	Signature_UV	Signature_UV	SBS7
#63	-	Signature_clock-like	Signature_clock	SBS5

Abbreviations: +: positive; -: negative

Supplementary Table S5. Copy Number Variations (CNVs) in melanoma driver genes detected by Whole-Exome Sequencing (WES) in common between the pre-therapy and post-therapy melanoma lesions.

Gene	CNV	Sample ID	*BRAF* V600 status	R
		#39	+	y
PTEN	DELETION	#34	-	n
		#63	-	n
FBXW7	DELETION	#63	-	n
KIT	DELETION	#63	-	n

		#34	-	n
DDX3X	DELETION			
		#63	-	n
BRAF	AMPLIFICATION	#18	-	n
		#21	-	y
KIT	AMPLIFICATION			
		#34	-	n
		#21	-	y
STK19	AMPLIFICATION	#7	-	y
		#34	-	n

		#21	-	y
EZH2	AMPLIFICATION	#34	-	n
		#18	-	n
NRAS	AMPLIFICATION	#34	-	n
MAP2K2	AMPLIFICATION	#34	-	n
RAC1	AMPLIFICATION	#34	-	n
SNX31	AMPLIFICATION	#34	-	n
TACC1	AMPLIFICATION	#34	-	n

TERT	AMPLIFICATION	#34		-	n
GNA11	AMPLIFICATION	#34		-	n

Abbreviations: R: Response; n: no; y: yes: -: Negative; +: Positive; CNV: Copy Number Variation.

Supplementary Table S6. Copy Number Variations (CNVs) in melanoma driver genes detected by Whole-Exome Sequencing (WES) acquired in the post-therapy melanoma lesions.

Gene	CNV	Sample ID	*BRAF* V600 status	R
		#39§	+	y
BRAF	AMPLIFICATION	#1§	+	n
		#20	-	y
		#1	+	n
HRAS	AMPLIFICATION	#20	-	y
		#34	-	n
CDK4	AMPLIFICATION	#1	+	n

KRAS	AMPLIFICATION	#18	-	n
MAP2K1	AMPLIFICATION	#20	-	y
MAP2K2	AMPLIFICATION	#42	+	y
		#1	+	n
GNA11	AMPLIFICATION	#1	+	n
		#42	+	y
		#20	-	y
EZH2	AMPLIFICATION	#42	+	y

		#20	-	y
		#57	-	n
FBXW7	AMPLIFICATION	#21	-	y
		#1	+	n
MTOR	AMPLIFICATION	#42	+	y
		#20	-	y
		#18	-	n
NRAS	AMPLIFICATION			
		#57	-	n

Gene	Type	Sample		
PPP6C	AMPLIFICATION	#1	+	n
		#20	-	y
RAC1	AMPLIFICATION	#1	+	n
		#42	+	y
		#20	-	y
RB1	AMPLIFICATION	#1	+	n
STK19	AMPLIFICATION	#1	+	n
		#42	+	y

TERT	AMPLIFICATION	#20	-	y
TP53	AMPLIFICATION	#20	-	y
WT1	AMPLIFICATION	#20	-	y
FBXW7	DELETION	#20	-	y
CDKN2A	DELETION	#20	-	y
CNOT9	DELETION	#20	-	y
CTNNB1	DELETION	#20	-	y
DDX3X	DELETION	#1	+	n

		#20	-	y
GNA11	DELETION	#63	-	n
		#57	-	n
HRAS	DELETION	#42	+	y
IDH1	DELETION	#20	-	y
MAP2K1	DELETION	#20	-	y
MAP2K2	DELETION	#63	-	n
		#57	-	n

TACC1	DELETION	#20	-	y
TP53	DELETION	#63	-	n

Abbreviations: R: Response; n: no; y: yes; -: Negative; +: Positive; CNV: Copy number variation; §: gain present in the pre-lesions and post lesion.

Supplementary Table S7. Loss Of Function (LOF) variants in DNA Damage Repair (DDR) genes.

For each of 36 patients, exonic somatic LOF variants in DDR genes with an Allele Frequency (AF) at least 10% are reported. In bold the variants found in common in the two lesions of the same patient.

Chr	*BRAF* V600 status	R	Gene	aa change	Ref seq	Coverage	AF
#2	+	y	*TP53BP1*	p.Ser1359fs	*NM_001141980.3*	*58*	*63.6*
#2	+	y	*DDB1*	p.Arg989fs	*NM_001923.5*	*45*	*42.9*
#17	+	y	*RAD51B*	p.Gln371*	*NM_133509.4*	*76*	*20.0*
#39_PRE	+	y	*TDG*	p.Ile98fs	*NM_003211.6*	*195*	*20.0*
#39_PRE	+	y	*CUL4B*	p.Ser61fs	*NM_003588.3*	*63*	*12.8*
#39	+	y	*CUL5*	p.Gln709*	*NM_003478.6*	*965*	*59.6*
#40	+	y	*MSH6*	p.Asp1026fs	*NM_000179.2*	*585*	*10.1*
#42	+	y	*ERCC6*	p.Ala298delinsGlyPheSerSerTerSerValProSer	*NM_000124.4*	*61*	*45.5*

#42	+	y	*MLH3*	p.Asn629fs	*NM_001040108.1*	*182*	*11.4*
#10	+	n	*MDC1*	p.Arg944fs	*NM_014641.3.5*	*202*	*12.5*
#10	+	n	*TP53BP1*	p.Ser1359fs	*NM_001141980.3*	*88*	*50.0*
#10	+	n	*POLM*	p.Arg248*	*NM_001284330.2*	*1488*	*30.3*
#10	+	n	*ERCC6*	p.Ala298delinsGlyPheSerSerTerSerValProSer	*NM_000124.4*	*85*	*66.7*
#14	+	n	*HERC2*	p.Gln142fs	*NM_004667.5*	*67*	*17.6*
#14	+	n	*TP53BP1*	p.Ser1359fs	*NM_001141980.3*	*83*	*20.0*
#14	+	n	*ERCC6*	p.Ala298delinsGlyPheSerSerTerSerValProSer	*NM_000124.4*	*92*	*26.9*
#14	+	n	*LIG4*	p.Thr554fs	*NM_001352604.1*	*173*	*23.0*
#14	+	n	*SHPRH*	p.Asp944fs	*NM_001042683.3*	*38*	*21.4*

#19	+	n	*PTEN*	p.Arg303fs	*NM_001085384.3*	*410*	*64.8*
#3	+	n	*CHEK2*	p.Ser499fs	*NM_001005735.2*	*83*	*23.5*
#3	+	n	*FANCE*	p.Arg176fs	*NM_021922.3*	*81*	*14.6*
#3	+	n	*TP53BP1*	p.Ser1359fs	*NM_001141980.3*	*60*	*25.0*
#3	+	n	*ERCC6*	p.Ala298delinsGlyPheSerSerTerSerValProSer	*NM_000124.4*	*71*	*37.5*
#3	+	n	*APEX2*	p.Thr295fs	*NM_014481*	*88*	*23.8*
#3	+	n	*FANCA*	p.Ala1215fs	*NM_000135.4*	*81*	*18.9*
#3	+	n	*TDP1*	p.Asp346fs	*NM_001008744.2*	*59*	*53.8*
#3	+	n	*SHPRH*	p.Glu131*	*NM_001042683.3*	*117*	*15.2*
#62_POST	+	n	*GEN1*	p.Lys839fs	*NM_001130009.3*	*368*	*45.0*

#62_POST	+	n	*PMS1*	p.Leu164fs	*NM_001321049.2*	*269*	*44.1*
#6	-	y	*RFC1*	p.Thr132fs	*NM_001204747.2*	*190*	*14.9*
#6	-	y	*TP53BP1*	p.Ser980_Gly981insIleArgGly	*NM_001141980.3*	*36*	*33.3*
#6	-	y	*ERCC6*	p.Ala298delinsGlyPheSerSerTerSerValProSer	*NM_000124.4*	*141*	*23.1*
#6	-	y	*APEX2*	p.Thr295fs	*NM_014481*	*88*	*15.6*
#6	-	y	*RBP1*	p.Ter158Glnext*?	*NM_001130992.2*	*45*	*18.2*
#20_PRE	-	y	*APEX2*	p.Thr295fs	*NM_014481*	*51*	*50.0*
#20_PRE	-	y	*ERCC6*	p.Ala298delinsGlyPheSerSerTerSerValProSer	*NM_000124.4*	*164*	*21.2*
#20_POST	-	y	*ERCC6*	p.Ala298delinsGlyPheSerSerTerSerValProSer	*NM_000124.4*	*115*	*41.2*
#20_POST	-	y	*LIG4*	p.Thr554fs	*NM_001352604.1*	*280*	*13.3*

#20_POST	-	y	*REV3L*	p.Lys1044delinsAsnLeuTrpAspLeuCysPheSerGlnLysGluAsnLeuValTerThrTerHisHisTyrAsnSer	*NM_001372078.1*	*101*	*23.1*
#20_POST	-	y	*DCLRE1B*	p.Lys290_Pro291insIleProValGlyProSerThrTerSerProSerPheGluThrHisArgLysAlaLeu	*NM_022836.4*	*115*	*20.0*
#20_POST	-	y	TP53BP1	p.Thr514fs	NM_001141980.3	129	16.7
#21	-	y	*GTF2H1*	p.Trp33*	*NM_001142307.1*	*109*	*12.0*
#21	-	y	*TDP2*	p.Thr230fs	*NM_016614.3*	*103*	*33.3*
#21	-	y	*BRCA1*	p.Ser377fs	*NM_007300.4*	*254*	*27.5*
#21	-	y	*TP53BP1*	p.Ser1359fs	*NM_001141980.3*	*138*	*21.7*
#21	-	y	*ATRX*	p.Ala1410fs	*NM_000489.5*	*89*	*23.5*
#21	-	y	*RAD54B*	p.Lys132*	*NM_012415.3*	*279*	*18.8*
#38	-	y	*BRCA2*	p.Glu954*	*NM_000059.3*	*376*	*34.5*

#46	-	y	ERCC6	p.Ala298delinsGlyPheSerSerTerSerValProSer	NM_000124.4	78	37.5
#59	-	y	BLM	p.Gln83*	NM_000057.4	688	11.1
#34_PRE	-	n	TDP2	p.Thr230fs	NM_016614.3	43	29.4
#34_PRE	-	n	MDC1	p.Val440_Leu441insAlaHisProGlyProProProHisGluLeuSerProAlaTerGluGlnLeuGlnProThrLeuProGlnHisPro	NM_014641.3.5	59	23.5
#34_PRE	-	n	BRCA1	p.Ser377fs	NM_007300.4	172	30.3
#34_PRE	-	n	TP53BP1	**p.Ser1359fs**	NM_001141980.3	68	26.9
#34	-	n	TP53BP1	**p.Ser1359fs**	NM_001141980.3	66	15.4
#34_PRE	-	n	CDC5L	p.Gly604fs	NM_001253.4	159	10.3
#34_PRE	-	n	ERCC6	**p.Ala298delinsGlyPheSerSerTerSerValProSer**	NM_000124.4	79	80.0
#34	-	n	ERCC6	**p.Ala298delinsGlyPheSerSerTerSerValProSer**	NM_000124.4	100	25.9

#34_PRE	-	n	*REV1*	p.Leu289fs	*NM_001321454.2*	*51*	*23.1*
#34_PRE	-	n	*LIG4*	**p.Thr554fs**	*NM_001352604.1*	*182*	*15.6*
#34	-	n	*LIG4*	**p.Thr554fs**	*NM_001352604.1*	*204*	*11.2*
#34	-	n	*FANCE*	p.Arg176fs	*NM_021922.3*	*95*	*17.2*
#34	-	n	*MLH3*	p.Asn629fs	*NM_001040108.1*	*218*	*11.8*
#34	-	n	*ATR*	p.Val2230fs	*NM_001184.4*	*68*	*21.9*
#63_PRE	-	n	*ERCC6*	**p.Arg1221***	*NM_000124.4*	*329*	*64.6*
#63	-	n	*ERCC6*	**p.Arg1221***	*NM_000124.4*	*340*	*65.4*

Abbreviations: -:Negative; +: Positive; y: Yes; n: No; AF: Allele Frequency.

Supplementary Table S8. Loss of heterozygosity (LOH) in in DNA Damage Repair (DDR) genes detected by Whole-Exome Sequencing (WES) in common between the pre-therapy and post-therapy melanoma lesions.

Gene	Sample ID	*BRAF* V600 status	R
APEX2	#39	+	y
	#63	-	n
ATRX	#39	+	y
	#63	-	n
BRCC3	#39	+	y
	#63	-	n
CETN2	#39	+	y
	#63	-	n
FANCB	#39	+	y
	#63	-	n
POLA1	#39	+	y
	#63	-	n
RPA4	#39	+	y
	#63	-	n
TREX2	#39	+	y
	#63	-	n
UBE2A	#39	+	y
	#63	-	n
ASCC3	#63	-	n
ATM	#63	-	n
CHEK1	#63	-	n
DCLRE1A	#63	-	n
DCLRE1C	#63	-	n
DNTT	#63	-	n
DUT	#63	-	n

ERCC6	#63	-	n
FANCA	#63	-	n
GTF2H5	#63	-	n
H2AFX	#63	-	n
HELQ	#63	-	n
HERC2	#63	-	n
HMGB2	#63	-	n
INO80	#63	-	n
MGMT	#63	-	n
MMS19	#63	-	n
NEIL3	#63	-	n
NSMCE4A	#63	-	n
PARG	#63	-	n
PLRG1	#63	-	n
POLL	#63	-	n
POLN	#63	-	n
PTEN	#63	-	n
RAD51	#63	-	n
REV3L	#63	-	n
RFC1	#63	-	n
RNF4	#63	-	n
SHPRH	#63	-	n
SMARCAD1	#63	-	n
TP53BP1	#63	-	n
TTK	#63	-	n
UVSSA	#63	-	n

Abbreviations: R: Response; Y: yes; N: no

Supplementary Table S9. Loss of heterozygosity (LOH) in DNA Damage Repair (DDR) genes detected by Whole-Exome Sequencing (WES) acquired in the post-therapy melanoma lesions.

Gene	Sample ID	*BRAF* V600 status	R
APEX2	#1	+	n
	#62	+	n
APTX	#21	-	y
	#62	+	n
ASCC3	#21	-	y
	#39	+	y
	#62	+	n
ATM	#21	-	y
	#39	+	y
	#62	+	n
ATRX	#1	+	n
	#62	+	n
BLM	#21	-	y
	#62	+	n
	#63	-	n
BRCA1	#1	+	n
	#62	+	n
	#21	-	y
BRCC3	#1	+	n
	#62	+	n
	#21	-	y
BRIP1	#62	+	n
	#21	-	y
CDC5L	#62	+	n
	#21	-	y
CETN2	#1	+	n

	#62	+	n
	#21	-	y
	#39	+	y
CHEK1	#62	+	n
	#62	+	n
CHEK2	#62	+	n
	#21	-	y
CUL5	#39	+	y
	#62	+	n
DCLRE1A	#39	+	y
	#62	+	n
DMC1	#62	+	n
	#21	-	y
DNA2	#39	+	y
	#62	+	n
DUT	#39	+	y
	#62	+	n
ENDOV	#62	+	n
	#21	-	y
ERCC6	#39	+	y
	#62	+	n
FAAP100	#62	+	n
	#21	-	y
	#1	+	n
FANCB	#62	+	n
	#21	-	y
FANCC	#62	+	n
	#21	-	y
FANCD2	#39	+	y
	#62	+	n
FANCE	#62	+	n
	#21	-	y

FANCF	#62	+	n
	#63	-	n
FANCG	#62	+	n
	#21	-	y
GADD45G	#62	+	n
	#21	-	y
	#39	+	y
GTF2H5	#62	+	n
	#21	-	y
H2AFX	#39	+	y
	#62	+	n
HERC2	#39	+	y
	#62	+	n
HUS1	#62	+	n
	#62	+	n
INO80	#39	+	y
	#62	+	n
MMS19	#39	+	y
	#62	+	n
NSMCE4A	#39	+	y
	#62	+	n
OGG1	#39	+	y
	#62	+	n
PARG	#39	+	y
	#62	+	n
PARP1	#39	+	y
	#62	+	n
	#1	+	n
POLA1	#62	+	n
	#21	-	y
POLE3	#62	+	n
	#21	-	y

POLH	#62	+	n
	#21	-	y
POLL	#39	+	y
	#62	+	n
PRKDC	#62	+	n
	#63	-	n
RAD18	#39	+	y
	#62	+	n
RAD23B	#62	+	n
	#21	-	y
RAD51C	#62	+	n
	#21	-	y
RAD52	#62	+	n
	#63	-	n
RBX1	#62	+	n
	#21	-	y
REV3L	#39	+	y
	#62	+	n
	#21	-	y
RMI1	#62	+	n
	#21	-	y
RNF4	#1	+	n
	#62	+	n
RNF8	#62	+	n
	#21	-	y
RPA4	#1	+	n
	#62	+	n
	#21	-	y
SETMAR	#39	+	y
	#62	+	n
SHPRH	#39	+	y
	#62	+	n

	#21	-	y
SMC5	#62	+	n
	#21	-	y
SOX4	#62	+	n
	#21	-	y
	#39	+	y
SPRTN	#62	+	n
SWI5	#62	+	n
	#21	-	y
TDP2	#62	+	n
	#21	-	y
TOP3B	#62	+	n
	#21	-	y
	#39	+	y
TP53BP1	#62	+	n
	#1	+	n
TREX2	#62	+	n
	#21	-	y
	#39	+	y
TTK	#62	+	n
	#21	-	y
	#1	+	n
UBE2A	#62	+	n
	#21	-	y
	#39	+	y
UBE2T	#62	+	n
UBE2V2	#62	+	n
	#63	-	n
XRCC6	#62	+	n
	#21	-	y
AEN	#62	+	n
ALKBH1	#62	+	n

ALKBH2	#62	+	n
ALKBH3	#62	+	n
APEX1	#62	+	n
APLF	#62	+	n
ATR	#62	+	n
BABAM1	#62	+	n
BARD1	#62	+	n
BCAS2	#62	+	n
BRCA2	#62	+	n
CCNH	#62	+	n
CDC25B	#62	+	n
CDC25C	#62	+	n
CHAF1A	#62	+	n
CUL3	#62	+	n
DCLRE1C	#62	+	n
DDB1	#62	+	n
DDB2	#62	+	n
DNTT	#39	+	y
EID3	#62	+	n
EME1	#21	-	y
EME2	#62	+	n
ERCC1	#62	+	n
ERCC2	#62	+	n
ERCC4	#62	+	n
ERCC5	#62	+	n
ERCC8	#62	+	n
EXO1	#39	+	y
EXO5	#62	+	n
FAAP20	#62	+	n
FAAP24	#62	+	n
FANCA	#39	+	y
FANCI	#62	+	n

FANCM	#62	+	n
FEN1	#62	+	n
GADD45A	#62	+	n
GEN1	#62	+	n
GTF2H3	#62	+	n
HELQ	#62	+	n
HES1	#62	+	n
HFM1	#62	+	n
HMGB1	#62	+	n
HMGB2	#62	+	n
IDH1	#62	+	n
LIG1	#62	+	n
LIG3	#62	+	n
LIG4	#62	+	n
MAD2L2	#62	+	n
MBD4	#62	+	n
MGMT	#39	+	y
MLH1	#62	+	n
MLH3	#62	+	n
MNAT1	#62	+	n
MORF4L1	#62	+	n
MPG	#62	+	n
MPLKIP	#62	+	n
MRPL40	#21	-	y
MSH2	#62	+	n
MSH3	#62	+	n
MSH6	#62	+	n
NABP2	#62	+	n
NBN	#62	+	n
NEIL2	#62	+	n
NEIL3	#62	+	n
NFATC2IP	#62	+	n

NHEJ1	#62	+	n
NSMCE1	#62	+	n
NTHL1	#62	+	n
NUDT15	#62	+	n
NUDT18	#62	+	n
PALB2	#62	+	n
PARP2	#62	+	n
PARP3	#62	+	n
PARP4	#62	+	n
PARPBP	#62	+	n
PAXIP1	#62	+	n
PER1	#62	+	n
PLK3	#62	+	n
PLRG1	#62	+	n
PMS1	#62	+	n
PMS2	#62	+	n
POLB	#62	+	n
POLD1	#62	+	n
POLD2	#62	+	n
POLD3	#62	+	n
POLD4	#62	+	n
POLE	#62	+	n
POLE2	#62	+	n
POLE4	#62	+	n
POLG	#62	+	n
POLI	#62	+	n
POLM	#62	+	n
POLQ	#62	+	n
PPP4C	#62	+	n
PPP4R1	#62	+	n
PPP4R2	#62	+	n
PRPF19	#62	+	n

PTEN	#39	+	y
RAD1	#62	+	n
RAD50	#62	+	n
RAD51	#39	+	y
RAD51B	#62	+	n
RAD51D	#62	+	n
RAD54B	#62	+	n
RAD9B	#62	+	n
RECQL4	#62	+	n
RECQL5	#21	-	y
REV1	#62	+	n
RFC1	#62	+	n
RFC2	#62	+	n
RFC3	#62	+	n
RFC4	#62	+	n
RFC5	#62	+	n
RIF1	#39	+	y
RMI2	#62	+	n
RNF168	#62	+	n
RNF169	#62	+	n
RNMT	#62	+	n
RPA1	#62	+	n
RPA2	#62	+	n
RPA3	#62	+	n
RRM1	#62	+	n
RRM2	#62	+	n
RRM2B	#62	+	n
RTEL1	#62	+	n
SLX1A	#62	+	n
SLX4	#62	+	n
SMARCAD1	#62	+	n
SMC6	#62	+	n

SMUG1	#62	+	n
SPO11	#62	+	n
TCEA1	#62	+	n
TDG	#62	+	n
TDP1	#62	+	n
TELO2	#62	+	n
TOP3A	#62	+	n
TOPBP1	#62	+	n
TP53	#62	+	n
TYMS	#62	+	n
UBE2B	#62	+	n
UBE2N	#62	+	n
UIMC1	#62	+	n
UNG	#62	+	n
USP1	#62	+	n
WDR48	#62	+	n
WRN	#62	+	n
XAB2	#62	+	n
XPA	#21	-	y
XPC	#62	+	n
XRCC1	#62	+	n
XRCC2	#62	+	n
XRCC3	#62	+	n
XRCC5	#62	+	n
YWHAB	#62	+	n
YWHAG	#62	+	n
ZSWIM7	#62	+	n

Abbreviations: R: Response; y: yes; n: no

Supplementary Table S10. Circulating free DNA (cfDNA) mutational profile.

Sample ID	Sex	R	Stage	*BRAF* V600 status	Previous treatment	Treatment	cfDNA-NGS results	AF%	Tissue-WES results	AF%	Time variation from tissue to cfDNA (days)	Time variation from therapy to cfDNA (days)
#2	M	Y	IV	+	Y	BRAF+MEKi	*BRAF* p.Val600Glu	4.8	*BRAF* p.Val600Glu	52.4	15	369
							NRAS p.Gln61Lys	5.0	-	-		
							CDK4 Amplification	1.3	*CDK4* Amplification	4 copies		
							-	-	*CCND3* amplification	3 copies		
							-	-	*CCND1* amplification	3 copies		
							-	-	*EGFR* amplification	3 copies		
							-	-	*FGFR3* amplification	4 copies		
							-	-	*FGFR2* deletion	1copy		
#17	F	Y	IV	+	Y	ICB	*BRAF* p.Val600Glu	0.3	*BRAF* p.Val600Glu	42.0	610	946
							-	-	*FGFR3* amplification	4 copies		
							-	-	*CCND1* amplification	3 copies		
#26	M	Y	IV	+	y	BRAF+MEKi	-	-	*BRAF* p.Val600Glu	8.0	39	482
							-	-	*FGFR3* amplification	3 copies		
#39	M	Y	IV	+	Y	BRAF+MEKi and ICB	*BRAF* p.Val600Glu	32.6	*BRAF* p.Val600Glu	97.0	137	1329
							-	-	*FGFR2* deletion	1 copy		
#1	M	N	IV	+	Y	BRAF+MEKi	*BRAF* p.Val600Glu	67.7	*BRAF* p.Val600Glu	77.0	19	245
							NRAS p.Gln61Lys	3.5	-	-		
							MAP2K2 p.Gln60Pro	0.9	-	-		
							MET Amplification	4.3	-	-		
							-	-	*CCND1* amplification	3 copies		
							-	-	*CCND3* amplification	3 copies		
							-	-	*CDK4* amplification	4 copies		
							-	-	*FGFR3* amplification	4 copies		
#3	F	N	IV	+	N	-	-	-	*BRAF* p.Val600Glu	16.7	16	0

ID	Sex		Stage			Treatment	Mutation	Value	Alteration	Value		
							SMO p.Pro641Ala	50	-	-		
							-	-	CCND1 amplification	3 copies		
							-	-	CDK4 amplification	3 copies		
							-	-	FGFR3 amplification	5 copies		
							-	-	EGFR amplification	3 copies		
#8_T1	M	N	IV	+	N	-	-	-	BRAF p.Val600Glu	22	14	0
							-	-	CCND1 amplification	3 copies		
							-	-	EGFR amplification	3 copies		
							-	-	FGFR3 amplification	3 copies		
#8_T2	M	N	IV	+	Y	BRAF+MEKi	BRAF p.Val600Glu	3.8	BRAF p.Val600Glu	22	271	257
							BRAF p.Val600Met	0.8	-	-		
							PDGFRA p.Ala633Thr	0.24	-	-		
#10	F	N	IV	+	Y	BRAF+MEKi and ICB	BRAF p.Val600Glu	8.8	BRAF p.Val600Glu	60.0	289	461
							GNA11 p.Gln209Leu	3.7	-	-		
							-	-	FGFR3 amplification	4 copies		
							-	-	EGFR amplification	3 copies		
							-	-	CDK6 amplification	3 copies		
							-	-	CCND3 amplification	3 copies		
							-	-	CCND1 amplification	4 copies		
#14	F	N	IV	+	Y	ICB	BRAF p.Val600Glu	2.4	BRAF p.Val600Glu	43.8	51	21
							PIK3CA p.Asn345Lys	1.2	-	-		
							-	-	CCND1 amplification	3 copies		
							-	-	EGFR amplification	3 copies		
							-	-	FGFR3 amplification	4 copies		
#19	M	N	IV	+	Y	BRAF+MEKi	BRAF p.Val600Glu	0.7	BRAF p.Val600Glu	36.4	83	56
							NRAS p.Gln61Arg	0.2	-	-		
							-	-	FGFR2 deletion	1 copy		
#60_T1	F	N	IIIB	+	N	BRAF+MEKi adjuvant	-	-	BRAF p.Val600Glu	76.0	28	569
#60_T2	F	N	IIIB	+	N	BRAF+MEKi adjuvant	-	-	BRAF p.Val600Glu	76.0	329	871
#60_T3	F	N	IIIB	+	N	BRAF+MEKi adjuvant	-	-	BRAF p.Val600Glu	76.0	656	1198
#62_T1	M	N	IV	+	N	-	BRAF p.Val600Glu	12.3	BRAF p.Val600Glu	22.8	0	0

ID	Sex	R	Stage		AF	Treatment	Mutation	AF	Mutation	AF		
							PIK3CA p.Glu545Lys	0.4	-	-		
#62_T2	M	N	IV	+	N	BRAF+MEKi	*BRAF* p.Val600Glu	39.2	*BRAF* p.Val600Glu	17.0		
							GNA11 p.Gln209Leu	15.7	-	-	-7	110
							PIK3CA p.Glu545Lys	1.3	-	-		
#7	F	Y	IV	-	N	ICB	*BRAF* p.Val600Glu	0.8	-	-		
							KIT p. Lys642Glu	0.5	-	-		
							MET p.Arg988Cys 5	51.8	-	-	825	1002
							-	-	*IDH1* p.Arg132Cys	23.0		
							-	-	*CCND3* amplification	3 copies		
#57	M	N	IV	-	Y	ICB adjuvant and Imatinib	*BRAF* p.Gly469Ala	46.7	*BRAF* p.Gly469Ala	58.7		
							KIT p.Lys642Glu	34.6	*KIT* p.Lys642Glu	47.0		
							EGFR amplifications	1.32 copies	*EGFR* amplifications	3 copies	-6	441
							CDK6 amplifications	1.42 copies	*CDK6* amplifications	3 copies		
							MET amplifications	1.31 copies	-	-		

Abbreviations: R: Response; Y: yes; N: no; AF: Allele Frequency; ICB: Immunological Checkpoint Blocking; BRAF+MEKi: BRAF and MEK inhibitors.

Supplementary Table S11. Clinical characteristics of the enrolled patients.

Patient ID	*BRAF* V600 Status	Adjuvant therapy	1st line therapy	RECIST BOR 1st line therapy	PFS 1st line therapy	2nd line therapy	RECIST BOR 2nd line therapy	PFS 2nd line therapy	iAEs (G3-G5)	CLINICAL BENEFIT		
										Adjuvant	TT	ICI
#1	+	No	BRAF+MEKi	SD	7,53	Anti-PD-1	PD	0,93	No	NA	0	0
#2	+	No	BRAF+MEKi	SD	11,10	Anti-PD-1	PD	2,93	No	NA	1	0
#3	+	No	BRAF+MEKi	PD	3,07	No	NA	NA	No	NA	0	NA

#8	+	No	BRAF+MEKi	SD	8,17	No	NA	NA	No	NA	0	NA
#10	+	No	BRAF+MEKi	SD	5,73	Anti-PD-1	PR	9,07	No	NA	0	1
#14	+	No	Anti-CTLA-4 + Anti-PD-1	PD	1,37	BRAF+MEKi	PD	4,73	Colitis (G4)	NA	0	0

#17	+	No	Anti-PD-1	SD	11,20	No	NA	NA	Pneumonia (G1)	NA	NA	1
#19	+	No	BRAF+MEKi	SD	4,20	Anti-PD-1	PD	0,37	No	NA	0	0
#26	+	No	BRAF+MEKi	PR	13,07	BRAF+MEKi	PD	5,43	No	NA	1	NA

#30	+	No	Anti-PD-1	PR	7,93	No	NA	NA	Vitiligo	NA	NA	1
									No			
#37	+	No	BRAF+MEKi	PR	20,33	Anti-PD-1	PD	1,46		NA	1	0
									No			
#39	+	No	BRAF+MEKi	PR	24,97	Anti-PD-1	SD	7,33		NA	1	1

									No			
#40	+	No	BRAF+MEKi	PR	19,63	Anti-PD-1	SD	12,2		NA	1	1
									No			
#42	+	No	BRAF+MEKi	PR	20,10	No	NA	NA		NA	1	NA
									No			
#43	+	Adjuvant with BRAF+MEKi	BRAF+MEKi	PR	4,90	No	NA	NA		0	0	NA

									No			
#50	+	No	Anti-PD-1	PD	1,00	BRAF+MEKi	PR	2,96		0	0	0
									No			
#56	+	Adjuvant with BRAF+MEKi	Anti-PD-1	PD	2,00	Chemotherapy	PD	1,93		0	NA	0
									No			
#60	+	Adjuvant with BRAF+MEKi	No	NA	NA	No	NA	NA		0	NA	NA

		Adjuvant with anti-PD-1								0		
#62	+	No	BRAF+MEKi	PR	3,60	Anti-PD-1	PD	1,2	No	NA	0	0
#4	-	No	Anti-CTLA-4	PD	5,27	Anti-PD-1	PR	13,1	Thyroiditis and hypophysitis	NA	NA	1

#6	-	No	Anti-PD-1	SD	10,30	Anti-CTLA-4	PR	6,76	No	NA	NA	1
#7	-	No	Anti-PD-1	PR	64,20	No	NA	NA	Bullous pemphigoid	NA	NA	1
#18	-	No	Anti-PD-1	PD	5,90	Chemotherapy	PD	0,77	No	NA	NA	0

#20	-	No	Anti-PD-1	SD	3,73	Anti-PD-1	CR	13,06	No	NA	NA	1
#21	-	Anti-PD-1 +/- anti-CTLA-4	No	NA	NA	No	NA	NA	Vitiligo	1	NA	NA
#32	-	No	Anti-PD-1	PD	9,33	Anti CTLA-4	PR	13,86	Vitiligo	NA	NA	1

#34	-	No	Anti-PD-1	PD	2,80	No	NA	NA	No	NA	NA	0
#38	-	No	Anti-PD-1	PD	4,57	Anti-CTLA-4	SD	10,86	Amylase and lipase	NA	NA	1
#45	-	No	Anti-PD-1	PD	1,53	No	NA	NA	No	NA	NA	0

#46	-	No	Anti-PD-1	PR	29,43	No	NONo	NA	Hypothyroidism and arthritis	NA	NA	1
#47	-	Adjuvant with anti-PD-1	c-Kit-i	PR	6,33	Anti-CTLA-4	PD	1,1	No	0	0	0
#54	-	Adjuvant with anti-PD-1	No	NA	NA	NA	NA	NA	Pancreatitis	0	NA	NA

#55	-	Adjuvant with anti-PD-1	Anti-CTLA-4	PD	3,80	NA	NA	NA	Diarrhea	0	NA	0
#57	-	Adjuvant with anti-PD-1	c-Kit-i	PR	8,03	Chemotherapy	PD	1,8	No	0	0	0
#59	-	Adjuvant with anti-PD-1	No	NA	NA	NA	NA	NA	No	1	NA	NA

#63	-	Adjuvant with anti-PD-1	Anti-PD-1	SD	4,47	NA	NA	NA	No	0	NA	1

Anti-PD-1: nivolumab, pembrolizumab; Anti-CTLA-4: ipilimumab; BRAF+MEKi: vemurafenib + cobimetinib, dabrafenib + trametinib, encorafenib + binimetinib; c-KITi: imatinib.

Abbreviations: PD: NA: Not Available; SD: Stable Disease; PR: Partial Response; CR: Complete Response; PD: Disease Progression: ICB: Immunological Checkpoint Blocking; BOR: Best Overall Response; PFS: Progression Free Survival: iAEs. immuno-related Adverse Events; O: No clinical Benefit; 1: Clinical Benefit.