

Supplementary Methods

Quantitative RT-PCR

Five pairs of patient-matched samples were of sufficient RNA for quantitative RT-PCR analysis. Total RNA from these samples was reverse transcribed (SuperScript VILO, Life Technologies) in triplicates. The resulting cDNA was analyzed by real-time PCR (Power SYBR Green, Life Technologies; Mastercycler Realplex 4, Eppendorf) for *SGK3*, *SGSM2*, *ELOVL2* and *GAPDH* transcripts following manufacturer's instructions. Relative expression levels of *SGK3*, *SGSM2* and *ELOVL2* were determined by normalizing the amounts of these transcripts to that of *GAPDH*. The sequences of primers used are listed below.

*SGK3*_forward: 5'-TGTAGATTGGTGGTGCCTTGG-3',
*SGK3*_reverse: 5'-CTCCTGGCCTCAAACCTTAGGG-3';
*SGSM2*_forward: 5'-CGCGATGCTCTCAATGATCTGC-3',
*SGSM2*_reverse: 5'-CCCTGCATCTCGATCATGTCACC-3';
*ELOVL2*_forward: 5'-ATCTGGTGGTGTGTCTTGAACCTGG-3',
*ELOVL2*_reverse: 5'-ATGGTGTGCGTGATGGTGAGC-3';
*GAPDH*_forward: 5'-CACCCACTCCTCCACCTTTG-3',
*GAPDH*_reverse: 5'-GAGGTCCACCACCCTGTTG-3'.

Effects of PI3K inhibition in tumor xenografts

Animal experiments were conducted under a Novartis Animal Care and Use Committee-approved protocol at the Novartis animal facility in Emeryville, CA. Briefly, on day 0, 5×10^4 A375^{Luc} cells resuspended in 20 uL phosphate buffered saline solution were injected intracerebroventricularly into athymic nude mice (female, 6-7 weeks of age, Harlan Laboratories). Starting from day 11, mice with brain metastases were orally given vehicle control

(twice a day), BKM120 (once a day), LGX818 (twice a day) or the combination of BKM120 and LGX818 (once/twice a day), with six mice in each treatment group. Treatments were stopped on day 107 and survival duration analyzed by the Kaplan-Meier method; survival curves were drawn in Prism 6.0 (Graphpad), and median survivals were calculated in SPSS Statistics 21 (IBM).

For western blot analysis, A375^{Luc} human melanoma cells were implanted subcutaneously (5,000,000 cells) or intracranially into nude mice. Subcutaneous tumors and tumor-bearing mouse brains were harvested 20 days after implantation. The brains were imaged for bioluminescence, and tumor-containing regions were subjected to serial coronal section. H&E slides were prepared from brain sections and subcutaneous tumors. After pathological review, regions with >50% viable tumor cells were isolated. Protein extraction and western blot analysis on tumor tissues were conducted as previously described (1, 2). The antibodies used in western blotting were the same as in RPPA (Table S4).

References

1. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490:61-70.
2. Gopal YN, Deng W, Woodman SE, Komurov K, Ram P, Smith PD, et al. Basal and treatment-induced activation of AKT mediates resistance to cell death by AZD6244 (ARRY-142886) in Braf-mutant human cutaneous melanoma cells. *Cancer Res*. 2010;70:8736-47.

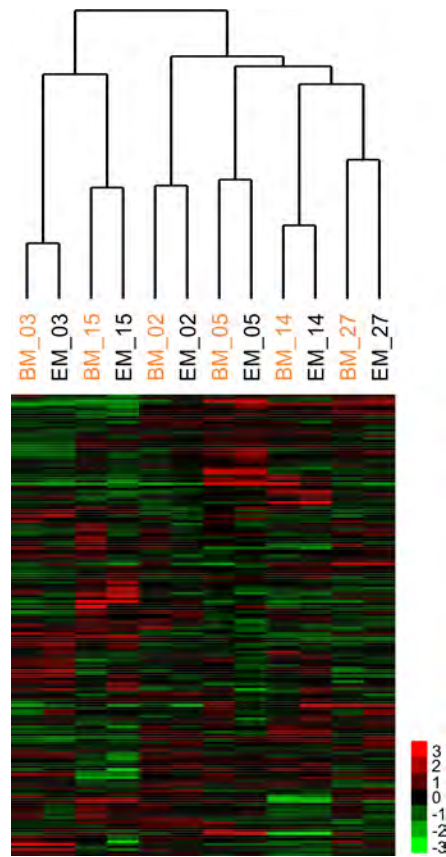


Fig. S1. Gene expression profiling of patient-matched brain and extracranial metastases. Log₂ expression values of 8050 probes in 6 brain metastases (BM, orange) and 6 extracranial metastases (EM, black) from the same patients are hierarchically clustered.

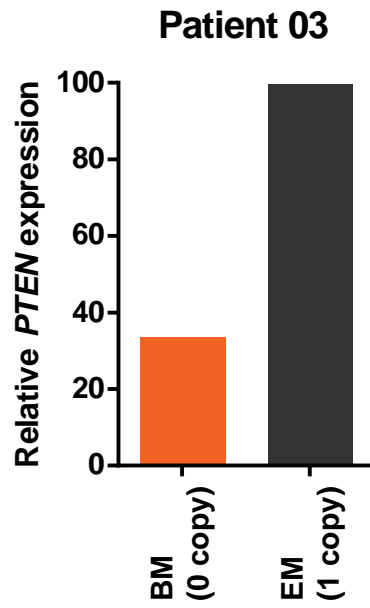


Fig. S2. PTEN gene expression in BM_03 (homozygous copy loss) and EM_03 (one copy loss). Gene expression was measured by microarray.

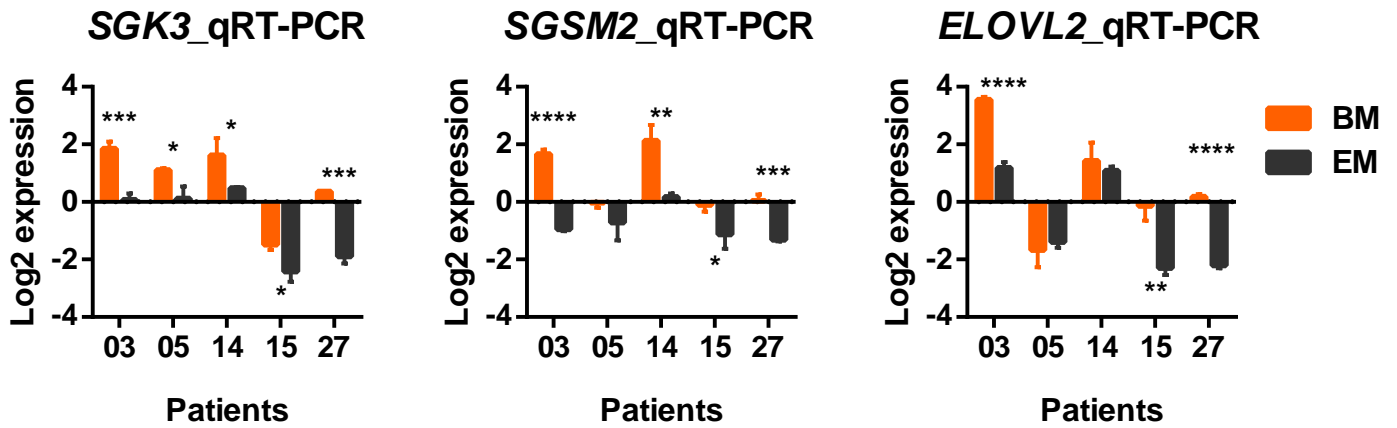


Fig. S3. Quantitative RT-PCR measurement of *SGK3*, *SGSM2* and *ELOVL2* expression in five pairs of brain metastases (BM) and extracranial metastases (EM). Each sample was measured in triplicates (supplementary methods). The differences in gene expression between BM and EM for each of the three genes measured are statistically significant ($P < 0.0001$ by two-way ANOVA). Asterisks indicate significant gene expression differences between patient-matched BM and EM samples (paired t -tests). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

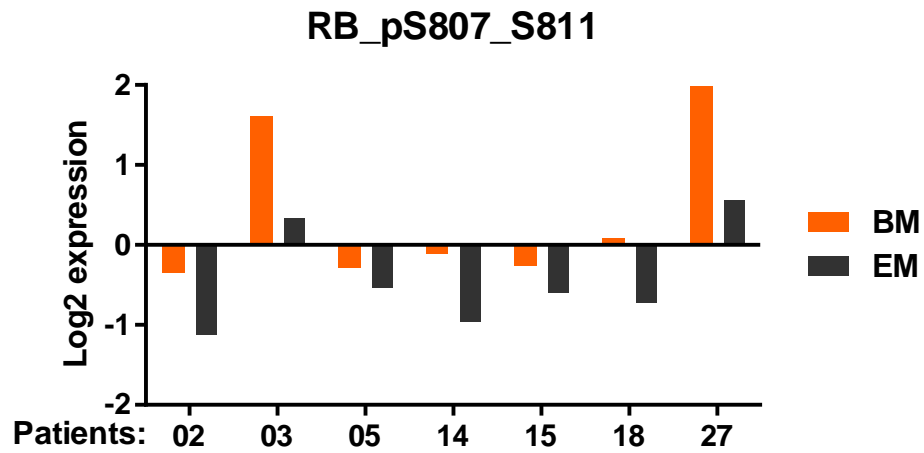


Fig. S4. Log2 expression levels of RB_pS807_S811 in seven pairs of matched metastases. Each column represents log2 expression value in one tumor. BM=brain metastasis, EM= extracranial metastasis

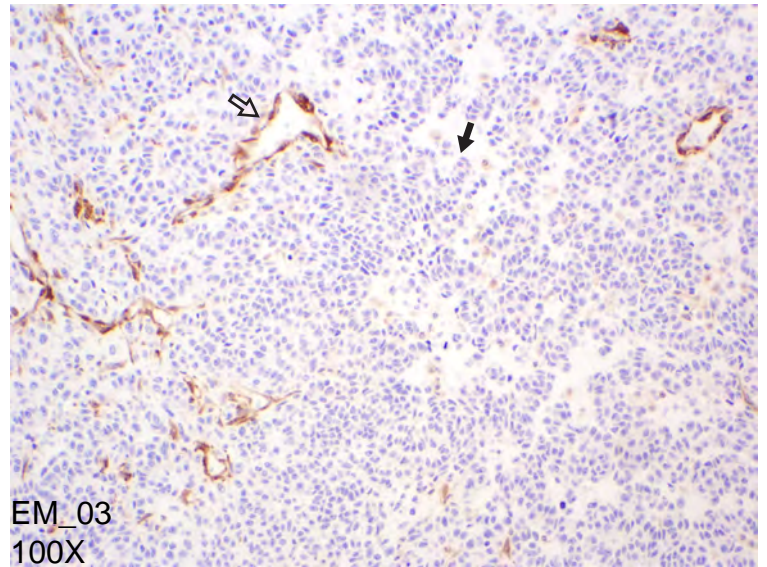
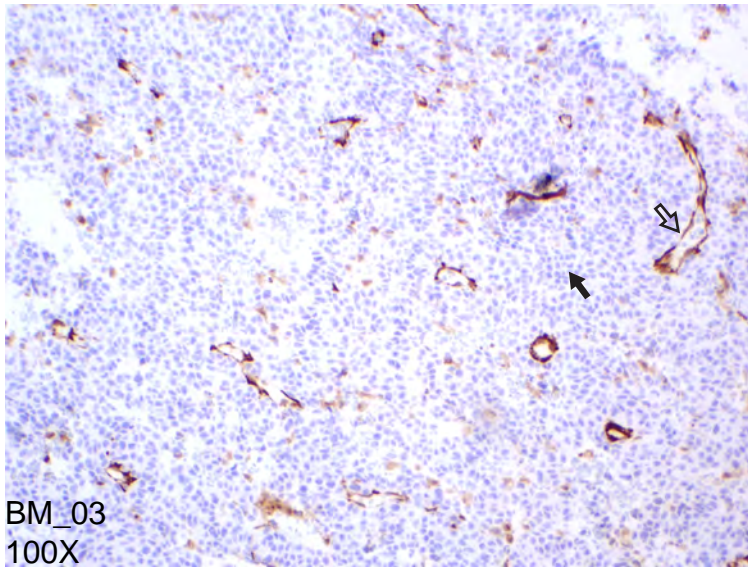


Fig. S5 Examples of PTEN-absent tumors. PTEN IHC of BM_03 and EM_03 were photographed at 100X magnification. Solid arrows point to tumor cells and open arrows point to vessels, which are internal controls for positive PTEN staining.

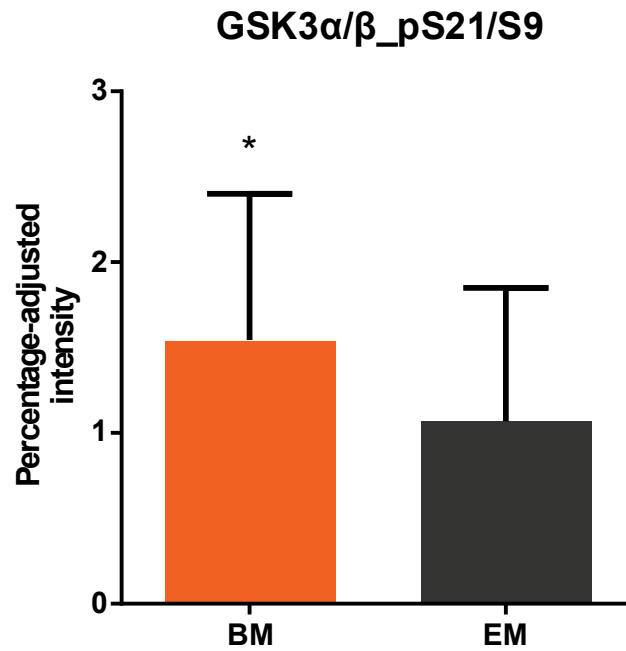
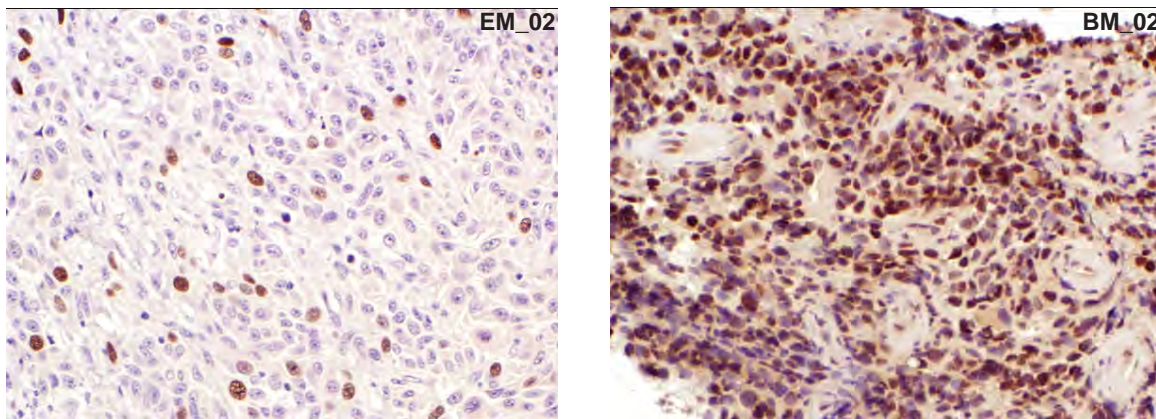


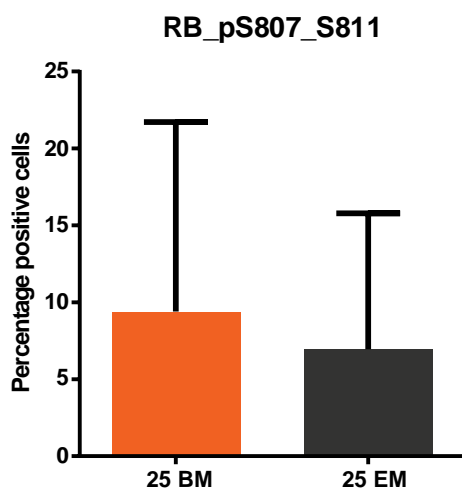
Fig. S6 GSK3 α / β _pS21/S9 IHC staining in 26 pairs of matched brain metastases (BM) and extracranial metastases (EM). Percentage-adjusted intensity was calculated for each tumor by multiplying the average staining intensity to the percentage of positively-stained tumor cells. The average and standard deviation of percentage-adjusted intensity in the 26 BM and the 26 EM are plotted. *, $P < 0.05$ in paired t-test.

A)

RB_pS807_S811 IHC



B)



C)

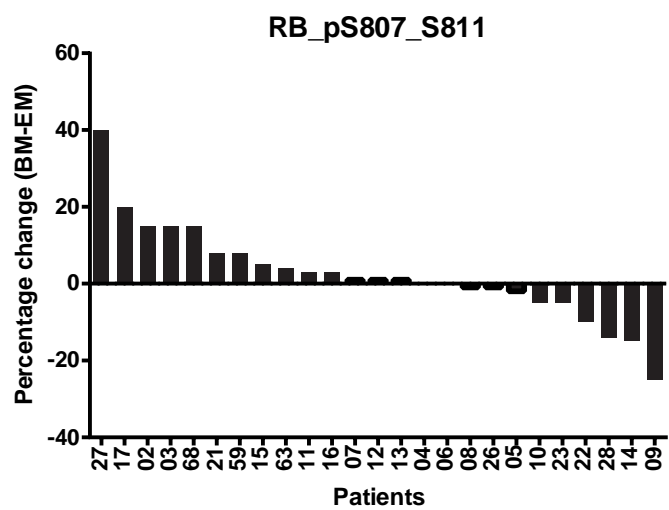


Fig.S7. Results of RB_pS807_S811 IHC in 25 pairs of matched brain metastases (BM) and extracranial metastases (EM). **(A)** Images of RB_pS807_S811 IHC in the BM and EM of patient 02. **(B)** Mean and standard deviation of the percentage of RB_pS807_S811 positive cells in 25 pairs of matched BM and EM. **(C)** The change in percentage of RB_pS807_S811 positive cells from EM to BM in each of the 25 patients. Left to right: the largest increase to the largest decrease.

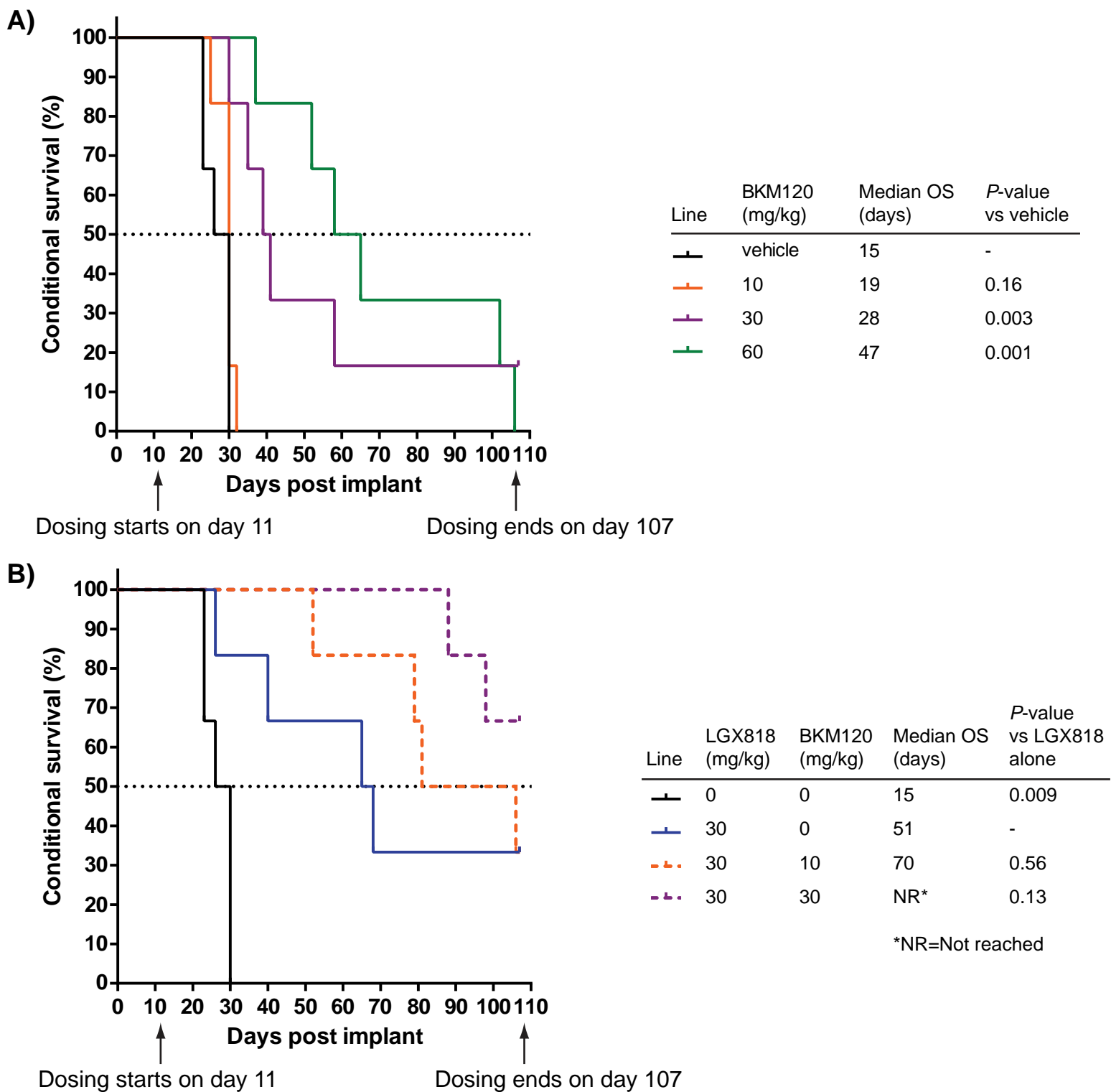


Fig. S8 Kaplan-Meier survival analysis of nude mice with BRAF-mutant melanoma brain metastases treated with BKM120 and/or LGX818. Indicated treatments were started 11 days after injection of BRAF-mutant human A375 melanoma cells, and after confirmation of successful tumor implantation. Mice were treated daily for up to 96 days, and were monitored for overall survival (OS). **(A)** Survival of mice treated with vehicle (black line), BKM120 10 mg/kg (orange), 30 mg/kg (purple), or 60 mg/kg (green). **(B)**, Survival of mice treated with vehicle (black line), LGX818 30 mg/kg alone (blue), LGX818 30mg/kg + BKM120 10 mg/kg (orange, dotted), or LGX818 30 mg/kg + BKM 30 mg/kg (purple, dotted).

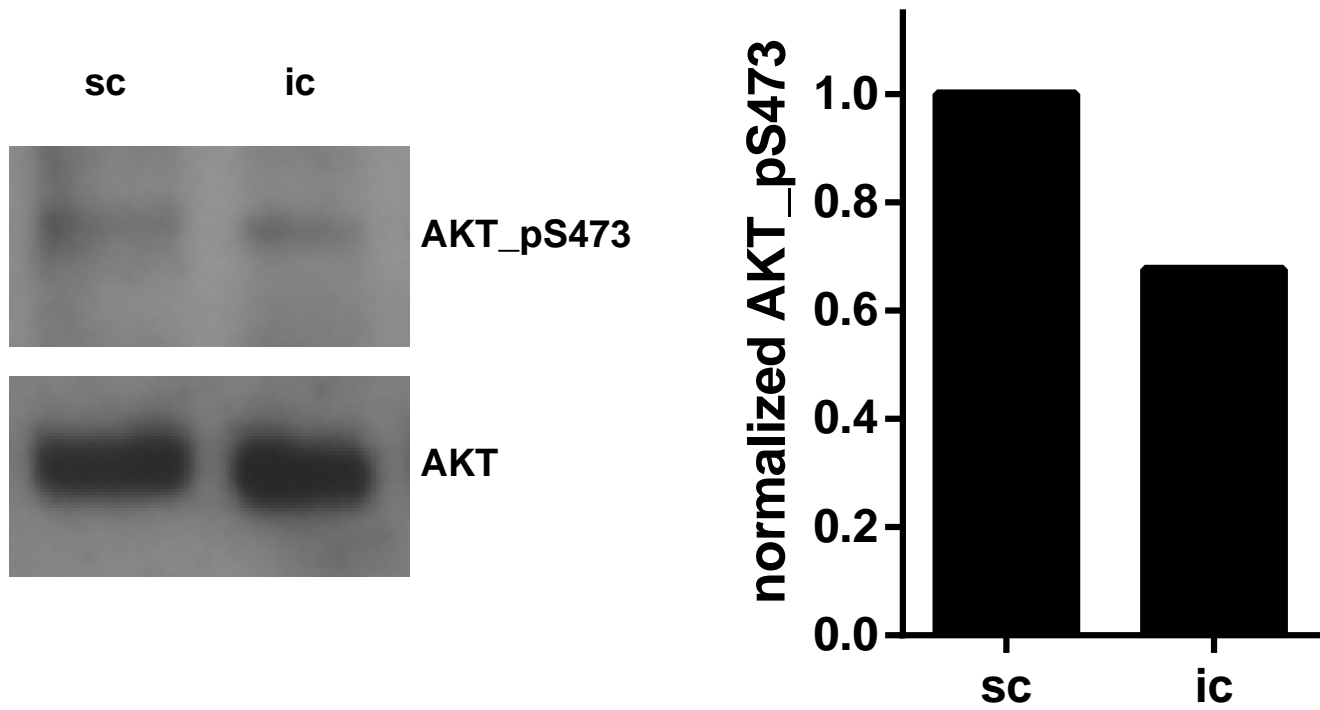


Fig. S9. AKT_pS473 level in subcutaneously (sc) and intracranially (ic) implanted melanomas. Left: western blot analysis of AKT_pS473 and AKT protein levels in A375 human melanoma xenografts. Right: quantitation results of western blot analysis, AKT_pS473 was normalized to AKT.

Table S1. List of clinical samples analyzed

Tumor	Patient	Matched or unmatched	Site	Sample type	Surgery date	Sequenom	CNV profiling	RNA profiling	RPPA	PTEN IHC	P-RB IHC	P-GSK3 IHC
BM_02	02	Matched	Brain	FFPE/Frozen	7/3/2003	Yes	No	Yes	Yes	Yes	Yes	No
EM_02	02	Matched	Lymph node	FFPE/Frozen	1/9/2004	Yes	No	Yes	Yes	Yes	Yes	No
BM_03	03	Matched	Brain	FFPE/Frozen	9/25/2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes
EM_03_A	03	Matched	Soft tissue	Frozen	2/28/2006	No	No	Yes	Yes	No	No	No
EM_03_B	03	Matched	Soft tissue	FFPE	3/9/2007	Yes	Yes	No	No	Yes	Yes	Yes
BM_04	04	Matched	Brain	FFPE	4/5/2006	Yes	Yes	No	No	Yes	No	Yes
EM_04	04	Matched	Small Intestine	FFPE/Frozen	3/8/2006	Yes	Yes	Yes	Yes	Yes	No	Yes
BM_05	05	Matched	Brain	FFPE/Frozen	10/18/2006	Yes	Yes	Yes	Yes	Yes	No	No
EM_05	05	Matched	Lymph node	FFPE/Frozen	4/10/2009	Yes	Yes	Yes	Yes	Yes	No	No
BM_06	06	Matched	Brain	FFPE	5/22/2006	Yes	No	No	No	Yes	No	No
EM_06_A	06	Matched	Small Intestine	FFPE	5/9/2003	Yes	No	No	No	Yes	No	No
EM_06_B	06	Matched	Small Intestine	Frozen	2/7/2005	No	No	Yes	Yes	No	No	No
BM_07	07	Matched	Brain	FFPE	5/1/2002	Yes	No	No	No	Yes	No	No
EM_07	07	Matched	Lymph node	FFPE	5/17/1999	Yes	No	No	No	Yes	No	No
BM_08	08	Matched	Brain	FFPE	9/17/2003	Yes	No	No	No	No	No	Yes
EM_08	08	Matched	Lymph node	FFPE/Frozen	6/26/2002	Yes	No	No	Yes	No	No	Yes
BM_09	09	Matched	Brain	FFPE	12/30/2010	Yes	Yes	No	No	Yes	No	No
EM_09	09	Matched	Lung	FFPE	8/17/2010	Yes	Yes	No	No	Yes	No	No
BM_10	10	Matched	Brain	FFPE	5/17/2010	Yes	Yes	No	No	Yes	No	Yes
EM_10	10	Matched	Lung	FFPE/Frozen	1/5/2009	Yes	Yes	Yes	Yes	Yes	No	Yes
BM_11	11	Matched	Brain	FFPE	10/13/1992	Yes	Yes	No	No	Yes	No	No
EM_11	11	Matched	Spleen	FFPE	3/24/1993	Yes	Yes	No	No	Yes	No	No
BM_12	12	Matched	Brain	FFPE	3/21/2001	Yes	Yes	No	No	Yes	No	No
EM_12	12	Matched	Lymph node	FFPE	9/28/1992	Yes	Yes	No	No	Yes	No	No
BM_13	13	Matched	Brain	FFPE/Frozen	3/25/1996	Yes	Yes	Yes	Yes	No	No	No
EM_13	13	Matched	Lung	FFPE	12/20/1994	Yes	Yes	No	No	No	No	No
BM_14	14	Matched	Brain	FFPE	4/30/2008	Yes	No	No	No	Yes	Yes	No
EM_14	14	Matched	Lymph node	FFPE	7/26/2006	Yes	No	No	No	Yes	Yes	No
BM_15	15	Matched	Brain	FFPE/Frozen	6/5/2009	Yes	Yes	Yes	Yes	Yes	Yes	No
EM_15	15	Matched	Soft tissue	FFPE/Frozen	4/11/2008	Yes	Yes	Yes	Yes	Yes	Yes	No
BM_16	16	Matched	Brain	FFPE/Frozen	9/23/1994	Yes	Yes	No	Yes	Yes	No	No
EM_16	16	Matched	Small Intestine	FFPE	3/28/1995	Yes	Yes	No	No	Yes	No	No
BM_17	17	Matched	Brain	FFPE	1/30/2007	Yes	No	No	No	Yes	No	No
EM_17	17	Matched	Lymph node	FFPE/Frozen	6/30/2005	Yes	No	Yes	Yes	Yes	No	No
BM_18	18	Matched	Brain	FFPE/Frozen	11/13/2008	No	No	No	Yes	No	No	No
EM_18	18	Matched	Bowel	FFPE/Frozen	6/25/2008	No	No	Yes	Yes	No	No	No
BM_20	20	Matched	Brain	FFPE/Frozen	10/16/1998	No	No	Yes	No	Yes	No	No
EM_20	20	Matched	Lymph node	FFPE	5/8/1998	No	No	No	No	Yes	No	No
BM_21	21	Matched	Brain	FFPE	4/8/2009	No	No	No	No	Yes	No	No
EM_21	21	Matched	Lung	FFPE/Frozen	1/23/2009	No	Yes	Yes	Yes	Yes	No	No
BM_22	22	Matched	Brain	FFPE	1/20/2010	No	No	No	No	Yes	No	No
EM_22	22	Unmatched	Spleen	FFPE/Frozen	8/3/2009	No	No	Yes	Yes	Yes	No	No
EM_23	23	Unmatched	Adrenal	Frozen	5/4/2001	No	No	Yes	Yes	No	No	No
EM_24	24	Unmatched	Spleen	FFPE/Frozen	9/20/2002	No	Yes	Yes	Yes	No	No	No
EM_25	25	Unmatched	Lymph Node	Frozen	8/6/2003	No	No	Yes	Yes	No	No	No
BM_26	26	Matched	Brain	FFPE	2/5/2007	No	No	No	No	Yes	No	No
EM_26	26	Matched	Lymph Node	FFPE/Frozen	12/12/2005	No	Yes	Yes	Yes	Yes	No	No

Tumor	Patient	Matched or unmatched	Site	Sample type	Surgery date	Sequenom	CNV profiling	RNA profiling	RPPA	PTEN IHC	P-RB IHC	P-GSK3 IHC
BM_27_A	27	Matched	Brain (right temporal)	FFPE/Frozen	10/19/2009	No	No	No	No	No	Yes	No
BM_27_B	27	Matched	Brain (right frontal)	Frozen	6/4/2009	No	No	Yes	Yes	No	No	No
EM_27_A	27	Matched	Soft tissue (back)	FFPE	3/14/2005	No	No	No	No	No	Yes	No
EM_27_B	27	Matched	Soft tissue (chest)	Frozen	10/22/2008	No	No	Yes	Yes	No	No	No
BM_28	28	Matched	Brain	FFPE	4/24/2003	No	No	No	No	Yes	No	No
EM_28	28	Unmatched	Bone	FFPE/Frozen	1/23/2002	No	Yes	Yes	Yes	Yes	No	No
EM_30	30	Unmatched	Lymph Node	Frozen	3/16/2005	No	No	Yes	No	No	No	No
EM_31	31	Unmatched	Lymph Node	Frozen	1/5/2005	No	No	Yes	No	No	No	No
EM_32	32	Unmatched	Lymph Node	Frozen	5/21/2004	No	No	Yes	No	No	No	No
EM_33	33	Unmatched	Lung	Frozen	5/6/2005	No	No	Yes	No	No	No	No
EM_34	34	Unmatched	Liver	Frozen	10/6/2003	No	No	Yes	No	No	No	No
EM_35	35	Unmatched	Lung	Frozen	6/2/2003	No	No	Yes	No	No	No	No
BM_36	36	Unmatched	Brain	Frozen	8/3/2005	No	No	Yes	No	No	No	No
BM_37	37	Unmatched	Brain	Frozen	8/24/2005	No	No	Yes	No	No	No	No
BM_38	38	Unmatched	Brain	Frozen	10/15/2008	No	No	Yes	No	No	No	No
BM_39	39	Unmatched	Brain	Frozen	10/10/2007	No	No	Yes	No	No	No	No
BM_40	40	Unmatched	Brain	Frozen	10/28/2008	No	No	Yes	No	No	No	No
BM_41	41	Unmatched	Brain	Frozen	9/18/2007	No	No	Yes	No	No	No	No
BM_42	42	Unmatched	Brain	Frozen	10/23/2007	No	No	Yes	No	No	No	No
EM_43	43	Unmatched	Brain	Frozen	6/26/2006	No	No	Yes	No	No	No	No
BM_44	44	Unmatched	Brain	Frozen	10/31/2007	No	No	Yes	No	No	No	No
BM_45	45	Unmatched	Brain	Frozen	10/1/2008	No	No	Yes	No	No	No	No
BM_46	46	Unmatched	Brain	Frozen	8/14/2009	No	No	Yes	No	No	No	No
BM_47	47	Unmatched	Brain	Frozen	1/28/2011	No	No	Yes	No	No	No	No
BM_48	48	Unmatched	Brain	Frozen	5/26/2010	No	No	Yes	No	No	No	No
BM_49	49	Unmatched	Brain	Frozen	3/16/2010	No	No	Yes	No	No	No	No
BM_50	50	Unmatched	Brain	Frozen	12/11/2009	No	No	Yes	No	No	No	No
BM_51	51	Unmatched	Brain	Frozen	9/20/2010	No	No	Yes	No	No	No	No
BM_52	52	Unmatched	Brain	Frozen	2/5/2010	No	No	Yes	No	No	No	No
BM_53	53	Unmatched	Brain	Frozen	8/23/2011	No	No	Yes	No	No	No	No
BM_54	54	Unmatched	Brain	Frozen	4/4/2011	No	No	Yes	No	No	No	No
BM_55	55	Unmatched	Brain	Frozen	11/10/2010	No	No	Yes	No	No	No	No
BM_57	57	Matched	Brain	FFPE	2/23/2009	No	No	No	No	Yes	No	Yes
EM_57	57	Matched	Small Intestine	FFPE	8/18/2010	No	Yes	No	No	Yes	No	Yes
BM_59	59	Unmatched	Brain	FFPE	7/10/2003	No	Yes	No	No	No	No	No
BM_60	60	Unmatched	Brain	FFPE	2/11/2003	No	Yes	No	No	No	No	No
EM_61	61	Unmatched	Small Intestine	FFPE	2/4/1998	No	Yes	No	No	No	No	No
BM_62	62	Unmatched	Brain	FFPE	4/1/1998	No	Yes	No	No	No	No	No
BM_63	63	Unmatched	Brain	FFPE	2/9/1998	No	Yes	No	No	No	No	No
BM_64	64	Unmatched	Brain	FFPE	4/20/2002	No	Yes	No	No	No	No	No
BM_65	65	Unmatched	Brain	FFPE	8/21/2001	No	Yes	No	No	No	No	No
BM_66	66	Unmatched	Brain	FFPE	12/5/2005	No	Yes	No	No	No	No	No
BM_67	67	Unmatched	Brain	FFPE	12/15/2008	No	Yes	No	No	No	No	No
BM_68	68	Matched	Brain	FFPE	10/13/1995	No	No	No	No	Yes	Yes	Yes
EM_68	68	Matched	Brain	FFPE	4/14/1995	No	No	No	No	Yes	Yes	Yes
BM_69	69	Matched	Brain	FFPE	6/15/2000	No	No	No	No	No	No	Yes
EM_69	69	Matched	Brain	FFPE	4/30/1999	No	No	No	No	No	No	Yes

Table S2. Clinical features and genetic aberrations of matched samples analyzed by high-throughput techniques

Patient	Site of extracranial sample	Days between sample acquisitions	Systemic therapies before sample acquisition	Systemic therapies between sample acquisitions	Radiation prior to brain surgery	BRAF/NRAS status		PTEN copy number		PTEN by IHC	
						BM	EM	BM	EM	BM	EM
* 02	Lymph node	190	None	Biochemo	No	BRAF ^{V600E}	BRAF ^{V600E}	n.a	n.a	absent	absent
* † 03	Soft tissue	374	Chemo,cilengitide	Chemo	No	WT	WT	homozygous loss	one copy loss	absent	absent
* † 04	Small Intestine	28	Chemo, high-dose IL-2	None	No	BRAF ^{V600E}	BRAF ^{V600E}	diploid	diploid	absent	absent
* † 05	Lymph node	905	None	None	No	BRAF ^{V600K}	BRAF ^{V600K}	one copy loss	one copy loss	absent	absent
* 06	Small Intestine	1109	Alloectin-7	None	No	NRAS ^{Q61K}	NRAS ^{Q61K}	n.a	n.a	n.a	n.a
* 07	Lymph node	1080	None	Vaccine	WBRT, 30Gy	BRAF ^{V600E}	BRAF ^{V600E}	n.a	n.a	present	present
* 08	Lymph node	448	None	biochemo, arsenic trioxide	No	NRAS ^{Q61K}	NRAS ^{Q61K}	n.a	n.a	n.a	n.a
* † 09	Lung	135	High-dose IL-2, biochemo, ipi	None	No	BRAF ^{V600E}	BRAF ^{V600E}	diploid	diploid	present	present
* † 10	Lung	497	None	None	No	WT	WT	one copy loss	one copy gain	present	present
* † 11	Spleen	162	None	None	No	BRAF ^{V600E}	BRAF ^{V600E}	one copy loss	one copy loss	present	present
* † 12	Lymph node	3096	None	Chemo, high-dose IL-2,	No	BRAF ^{V600E}	BRAF ^{V600E}	one copy loss	one copy loss	present	present
* † 13	Lung	461	None	Chemo	No	WT	WT	diploid	diploid	n.a	n.a
* 14	Lymph node	644	None	None	No	WT	WT	n.a	n.a	present	present
* † 15	Soft tissue	420	None	Biochemo, chemo	No	BRAF ^{V600E}	BRAF ^{V600E}	one copy loss	one copy loss	absent	absent
* † 16	Small Intestine	186	None	None	WBRT, 30Gy	WT	WT	one copy loss	one copy loss	present	absent
* 17	Lymph node	579	High-dose IFN γ	Chemo	SRS, 18Gy	NRAS ^{Q61H}	NRAS ^{Q61H?}	n.a	n.a	present	present
18	Bowel	141	Chemo, sorafenib and temsirolimus, ipi	Chemo	SRS, 20Gy	n.a	n.a	n.a	n.a	n.a	n.a
27	Soft tissue	1543	IFN, biochemo, ipi	None	No	n.a	n.a	n.a	n.a	n.a	n.a

chemo=chemotherapy

biochemo=biochemotherapy

ipi=ipilimumab

IFN=interferon

WBRT=whole brain radiation

SRS=steorotactic radiosurgery

* Hotspot mutations profiled by Sequenom

† CNV profiled

Frozen samples subjected to RNA and/or protein extraction are highlighted

 Analyzed by RPPA but not RNA microarray

 Analyzed by both RPPA and RNA microarray

BM=brain metastasis

EM=extracranial metastasis

Table S3. Hotspot mutations analyzed by Sequenom

Number	Assay.name.(gene_amino.acid_nucleotide)
1	AKT1_E17K_G49A
2	AKT1_G173R_G517C
3	AKT1_K179M_A536T
4	AKT2_E17K_G49A
5	AKT2_G175R_G523C
6	AKT3_E17K_G49A
7	AKT3_G171R_G511A
8	ALK_F1174L_C3522AG
9	ALK_F1174LIV_T3520CAG
10	ALK_F1245C_T3734G
11	ALK_F1245VI_T3733GA
12	ALK_I1171N_T3512A
13	ALK_R1275QL_G3824AT
14	BRAF_D594GV_A1781GT
15	BRAF_E586K_G1756A
16	BRAF_G464EVA_G1391ATC
17	BRAF_G466EVA_G1397ATC
18	BRAF_G466R_G1396CA
19	BRAF_G469EVA_G1406ATC
20	BRAF_G469R_G1405CA
21	BRAF_K601E_A1801G
22	BRAF_L597R_T1790G
23	BRAF_V600_G1800
24	BRAF_V600EAG_T1799ACG_F
25	BRAF_V600EAG_T1799ACG_R
26	BRAF_V600LM_G1798TA
27	CDK4_R24C_C70T
28	CDK4_R24H_G71A
29	CTNNB1_D32AGT_A95CGV
30	CTNNB1_D32HNY_G94CAT
31	CTNNB1_G34EVA_G101ATC
32	CTNNB1_S33APT_T97GCA
33	CTNNB1_S37APT_T109GCA
34	CTNNB1_S37CFY_C110GTA
35	CTNNB1_S45APT_T133GCA
36	CTNNB1_S45CFY_C134GTA
37	CTNNB1_T41APS_A121GCS
38	EGFR_G719_G2155TA
39	EGFR_K860I_A2579T
40	EGFR_L858R_T2573G
41	EGFR_L861_T2582AG
42	EGFR_S720P_T2158C
43	EGFR_T790M_C2369T
44	EGFR_T854I_C2561T
45	EGFR_Y813C_A2438G

Number	Assay.name.(gene_amino.acid_nucleotide)
46	EPHA3_K761N_G2283
47	FBWX7_R465C_C1393T
48	FBWX7_R465HL_G1394AT
49	FBWX7_R479QL_G1436AT
50	FBWX7_R505CS_C1513TA
51	FBWX7_R505HLP_G1514ATC
52	FGFR2_N549KK_T1647GA
53	FGFR2_S252W_C755G
54	FGFR3_G370C_G1108T
55	FGFR3_G697C_G2089T
56	FGFR3_K650EQ_A1948GC
57	FGFR3_K650MT_A1949TC
58	FGFR3_R248C_C742T
59	FGFR3_S249C_C746G
60	FGFR3_S371C_A1111T
61	FGFR3_Y373C_A1118G
62	FOXL2_C134W_C402G
63	FRAP_R2505P_G7514C
64	FRAP_S2215Y_C6644T
65	GNA11_Q209LP_A626TC
66	GNAQ_Q209H_A627T
67	GNAS_R201H_G602A
68	GNAS_R201SC_C601AT
69	IDH1_R132CGS_C394TGA
70	IDH1_R132HL_G395AT
71	IDH2_R140LQ_G419TA
72	IDH2_R140W_C418T
73	IDH2_R140W_C419T
74	IDH2_R172GW_A514GT
75	IDH2_R172MK_G515TA
76	IDH2_R172S_G516T
77	JAK2_V617F_G1849T
78	KIT_D816GVA_A2447GTC
79	KIT_D816HNY_G2446CAT
80	KIT_K642E_A1924G
81	KIT_L576P_T1727C
82	KIT_N566D_A1696G
83	KIT_N822KNK_T2466GCA
84	KIT_N822YHD_A2464TCG
85	KIT_R634W_C1900T
86	KIT_V559ADG_T1676CAG
87	KIT_V560D_T1679A
88	KIT_V825A_T2474C
89	KIT_Y553N_T1657A
90	KRAS_A146PT_G436CA
91	KRAS_G10R_G28A

Number	Assay.name.(gene_amino.acid_nucleotide)
92	KRAS_G12DAV_G35ACT
93	KRAS_G12SRC_G34ACT
94	KRAS_G13DAV_G38ACT
95	KRAS_G13SRC_G37ACT
96	KRAS_Q61EKX_C181GAT
97	KRAS_Q61HHE_A183CTG
98	KRAS_Q61LPR_A182TCG
99	MET_H1112_A3335GT
100	MET_H1112Y_C3334T
101	MET_M1268T_T3803C
102	MET_N375S_A1124G
103	MET_R988C_C2962T
104	MET_T1010I_C3029T
105	MET_Y1248C_A3743G
106	MET_Y1248HD_T3742CG
107	NRAS_A146T_G436A
108	NRAS_G12DAV_G35ACT
109	NRAS_G12SRC_G34ACT
110	NRAS_G13DAV_G38ACT
111	NRAS_G13SRC_G37ACT
112	NRAS_Q61EKX_C181GAT
113	NRAS_Q61HHQ_A183TCG
114	NRAS_Q61RPL_A182GCT
115	PDGFRA_D842_G2524TA
116	PDGFRA_D842V_A2525T
117	PDGFRA_N659K_C1977A
118	PDGFRA_N659Y_A1975T
119	PDGFRA_V561D_T1682A
120	PDPK1_D527E_C1581G
121	PDPK1_T354M_C1061T
122	PIK3CA_A1046V_C3137T
123	PIK3CA_E110K_G328A
124	PIK3CA_E418K_G1252A
125	PIK3CA_E453K_G1357A
126	PIK3CA_E542KQ_G1624AC
127	PIK3CA_E542VG_A1625TG
128	PIK3CA_E545AGV_A1634CGT
129	PIK3CA_E545D_G1635CT
130	PIK3CA_E545KQ_G1633AC
131	PIK3CA_F909L_C2727G
132	PIK3CA_H1047RL_A3140GT
133	PIK3CA_H1047RL_A3140GT.[1]
134	PIK3CA_H1047Y_C3139T
135	PIK3CA_H701P_A2102C
136	PIK3CA_K111N_G333C
137	PIK3CA_M1043I_G3129ATC

Number	Assay.name.(gene_amino.acid_nucleotide)
138	PIK3CA_M1043V_A3127G
139	PIK3CA_N345K_T1035A
140	PIK3CA_P539R_C1616G
141	PIK3CA_Q060K_C178A
142	PIK3CA_Q546EK_C1636GA
143	PIK3CA_Q546LPR_A1637TCG
144	PIK3CA_R088Q_G263A
145	PIK3CA_T1025SA_A3073TG
146	PIK3CA_Y1021C_A3062G
147	PIK3CA_Y1021HN_T3061CA
148	PIK3R1_D560Y_G1678T
149	PIK3R1_N564K_C1693AG
150	PRKAG1_R70Q_G209A
151	PRKAG2_N488I_A1463T
152	RET_M918T_T2753C
153	TNK2_E346K_G1036A
154	TNK2_R99Q_G296A

Table S4. Antibodies used in RPPA analysis

Ab Name	Gene Name	Company	Catalog #	Ab ID	Species	Validation Status*
14-3-3 beta	YWHAB	Santa Cruz	sc-628	882.	Rabbit	Validated
14-3-3 epsilon	YWHAE	Santa Cruz	sc-23957	913.1	Mouse	Use with Caution
14-3-3 zeta	YWHAZ	Santa Cruz	sc-1019	883.	Rabbit	Validated
4E-BP1	EIF4EBP1	CST	9452	2.8	Rabbit	Validated
4E-BP1_pS65	EIF4EBP1	CST	9456	3.1	Rabbit	Validated
4E-BP1_pT37_T46	EIF4EBP1	CST	9459	6.4	Rabbit	Validated
53BP1	TP53BP1	CST	4937	985.1	Rabbit	Validated
ACC_pS79	ACACA ACACB	CST	3661	13.4	Rabbit	Validated
ACC1	ACACA	Epitomics	1768-1	14.1	Rabbit	Under evaluation
ACVRL1	ACVRL1	Epitomics	2940-1	1086.10	Rabbit	Use with Caution
Akt	AKT1 AKT2 AKT3	CST	4691	1084.11	Rabbit	Validated
Akt_pS473	AKT1 AKT2 AKT3	CST	9271	23.10	Rabbit	Validated
Akt_pT308	AKT1 AKT2 AKT3	CST	2965	1154	Rabbit	Validated
AMPK_alpha	PRKAA1	CST	2532	39.4	Rabbit	Use with Caution
AMPK_pT172	PRKAA1	CST	2535	40.6	Rabbit	Validated
Annexin_VII	ANXA7	BD Biosciences	610668	1142.1	Mouse	Validated
AR	AR	Epitomics	1852-1	756.1	Rabbit	Validated
Bad_pS112	BAD	CST	9291	63.7	Rabbit	Validated
Bak	BAK1	Epitomics	1542-1	71.2	Rabbit	Use with Caution
Bax	BAX	CST	2772	73.5	Rabbit	Validated
Bcl-2	BCL2	Dako	Dako M0887	80.1	Mouse	Validated
Bcl-xL	BCL2L1	CST	2762	85.5	Rabbit	Validated
Beclin	BECN1	Santa Cruz	sc-10086	87.1	Goat	Use with Caution
beta-Catenin	CTNNB1	CST	9562	75.3	Rabbit	Validated
Bid	BID	Epitomics	1008-1	88.1	Rabbit	Use with Caution
Bim	BCL2L11	Epitomics	1036-1	90.1	Rabbit	Validated
B-Raf	BRAF	Santa Cruz	sc-5284	96.2	Mouse	Use with Caution
BRCA2	BRCA2	CST	9012	761.1	Rabbit	Use with Caution
Caspase-7_cleavedD198	CASP7	CST	9491	109.6	Rabbit	Use with Caution
Caveolin-1	CAV1	CST	3238	114.1	Rabbit	Validated
CD31	PECAM1	Dako	M0823	127.1	Mouse	Validated
CD49b	ITGA2	BD Biosciences	611016	937.1	Mouse	Validated
CDK1	CDC2	CST	9112	1007.5	Rabbit	Validated
Chk1	CHEK1	CST	2360	1203.3	Mouse	Use with caution
Chk1_pS345	CHEK1	CST	2348	903.7	Rabbit	Use with caution
Chk2	CHEK2	CST	3440	146.1	Mouse	Validated
Chk2_pT68	CHEK2	CST	2197	147.2	Rabbit	Use with Caution
cIAP	BIRC2	Millipore	07-759	930.1	Rabbit	Caution
c-Jun_pS73	JUN	CST	9164	155.5	Rabbit	Validated
c-Kit	KIT	Epitomics	1522	157	Rabbit	Validated
Claudin-7	CLDN7	Novus	NB100-91714	852.1	Rabbit	Validated
c-Met_pY1235	MET	CST	3129	727.5	Rabbit	Validated
c-Myc	MYC	Santa Cruz	sc-764	1143.1	Rabbit	Use with Caution
Collagen_VI	COL6A1	Santa Cruz	SC-20649	171.1	Rabbit	Validated
C-Raf	RAF1	Millipore	05-739	803	Rabbit	Validated
C-Raf_pS338	RAF1	CST	9427	179.4	Rabbit	Validated
Cyclin_B1	CCNB1	Epitomics	1495-1	192.1	Rabbit	Validated
Cyclin_D1	CCND1	Santa Cruz	SC-718	194.1	Rabbit	Validated
Cyclin_E1	CCNE1	Santa Cruz	SC-247	201.1	Mouse	Validated
DJ-1	PARK7	Abcam	ab76008	891.1	Rabbit	Validated
Dvl3	DVL3	CST	3218	940.1	Rabbit	Validated
E-Cadherin	CDH1	CST	3195	1099.10	Rabbit	Validated
eEF2	EEF2	CST	2332	1060.3	Rabbit	Use with Caution
eEF2K	EEF2K	CST	3692	1061.2	Rabbit	Validated
EGFR	EGFR	CST	2232	1120.15	Rabbit	Validated
EGFR_pY1068	EGFR	CST	2234	217.13	Rabbit	Use with caution; also sees pHer2
EGFR_pY1173	EGFR	Epitomics	1124	221.3	Rabbit	Validated
eIF4E	EIF4E	CST	9742	722.3	Rabbit	Validated
eIF4G	EIF4G1	CST	2498	1124.3	Rabbit	Use with Caution

ER-alpha	ESR1	Lab Vision	RM-9101-S	238.6	Rabbit	Validated
ER-alpha_pS118	ESR1	Epitomics	1091-1	241.1	Rabbit	Validated
FASN	FASN	Cell Signaling	3180	1156.00	Rabbit	Validated
Fibronectin	FN1	Epitomics	1574-1	262.1	Rabbit	Validated
FOXO3a	FOXO3	CST	2497	1122.6	Rabbit	Use with Caution
FOXO3a_pS318_S321	FOXO3	CST	9465	270.1	Rabbit	Use with Caution
FoxM1	FOX1	CST	5436	1123.1	Rabbit	Validated
G6PD	G6PD	Santa Cruz	sc-373887	1155	Mouse	Validated
Gab2	GAB2	CST	3239	943.1	Rabbit	Validated
GAPDH	GAPDH	Ambion	AM4300	274.11	Mouse	Caution
GATA3	GATA3	BD Biosciences	558686	764.1	Mouse	Validated
GSK3_pS9	GSK3A GSK3B	CST	9336	1082.12	Rabbit	Validated
GSK3-alpha-beta	GSK3A GSK3B	Santa Cruz	SC-7291	284.2	Mouse	Validated
GSK3-alpha-beta_pS21_S9	GSK3A GSK3B	CST	9331	285.12	Rabbit	Validated
HER2	ERBB2	Lab Vision	MS-325-P1	1038.2	Mouse	Validated
HER2_pY1248	ERBB2	R&D Systems	AF1768	1075.1	Rabbit	Use with caution; likely sees pEGFR
HER3	ERBB3	Santa Cruz	sc-285	911.1	Rabbit	Validated
HER3_pY1289	ERBB3	CST	4791	728.12	Rabbit	Use with Caution
Heregulin	NRG1	CST	2573	890.1	Rabbit	Validated
IGFBP2	IGFBP2	CST	3922	335.1	Rabbit	Validated
INPP4B	INPP4B	CST	4039	1065.1	Rabbit	Validated
IRS1	IRS1	Upstate (Millipore)	06-248	802.1	Rabbit	Validated
JNK_pT183_pY185	MAPK8	CST	4668	888.5	Rabbit	Validated
JNK2	MAPK9	CST	4672	380.1	Rabbit	Use with Caution
Lck	LCK	CST	2752	397.2	Rabbit	Validated
MAPK_pT202_Y204	MAPK1 MAPK3	CST	4377	405.3	Rabbit	Validated
MEK1	MAP2K1	Epitomics	1235-1	417.1	Rabbit	Validated
MEK1_pS217_S221	MAP2K1	CST	9154	1076.3	Rabbit	Validated
MIG-6	ERRFI1	Sigma	WH0054206M1	1062.1	Mouse	Validated
mTOR	FRAP1	CST	2983	444.3	Rabbit	Validated
mTOR_pS2448	FRAP1	CST	2971	446.14	Rabbit	Use with caution
MYH11	MYH11	SDI / Novus	21370002	1139.1	Rabbit	Validated
Myosin IIa_pS1943	MYH9	CST	5026	1160	Rabbit	Validated
N-Cadherin	CDH2	CST	4061	452.1	Rabbit	Validated
NDRG1_pT346	NDRG1	CST	3217	1126	Rabbit	Validated
NF2	NF2	SDI	2271.00.02	1046.1	Rabbit	Use with Caution
NF-kB-p65_pS536	NFKB1	CST	3033	457.4	Rabbit	Use with Caution
Notch1	NOTCH1	CST	3268	1064.1	Rabbit	Validated
N-Ras	NRAS	Santa Cruz	sc-31	1136.1	Mouse	Validated
p21	CDKN1A	Santa Cruz	SC-397	470.1	Rabbit	Validated
p27	CDKN1B	Epitomics	1591-1	897.1	Rabbit	Validated
p27_pT157	CDKN1B	R&D	AF1555	842.1	Rabbit	Use with Caution
p27_pT198	CDKN1B	Abcam	ab64949	878.1	Rabbit	Validated
p38_MAPK	MAPK14	CST	9212	478.10	Rabbit	Validated
p38_pT180_Y182	MAPK14	CST	9211	479.15	Rabbit	Validated
p53	TP53	CST	9282	481.3	Rabbit	Under evaluation
p70S6K	RPS6KB1	Epitomics	1494-1	493.1	Rabbit	Validated
p70S6K_pT389	RPS6KB1	CST	9205	494.7	Rabbit	Validated
p90RSK	RPS6KA1	CST	9347	759.5	Rabbit	Caution
p90RSK_pT359_S363	RPS6KA1	CST	9344	770.2	Rabbit	Use with Caution
Paxillin	PXN	Epitomics	1500-1	505.1	Rabbit	Caution
PCNA	PCNA	Abcam	ab29	511.1	Mouse	Caution
PDCD4	PDCD4	Rockland	600-401-965	816.1	Rabbit	Use with Caution
PDK1	PDK1	CST	3062	515.5	Rabbit	Validated
PDK1_pS241	PDK1	CST	3061	516.7	Rabbit	Validated
PEA15	PEA15	CST	2780	1017.2	Rabbit	Validated
PEA15_pS116	PEA15	Invitrogen	44-836G	1018.1	Rabbit	Validated
PI3K-p110-alpha	PIK3CA	CST	4255	808.1	Rabbit	Use with Caution
PI3K-p85	PIK3R1	Upstate (Millipore)	06-195	523.3 or 523.4	Rabbit	Validated
PKC-alpha	PRKCA	Upstate (Millipore)	05-154	529.1	Mouse	Validated
PKC-alpha_pS657	PRKCA	Upstate (Millipore)	06-822	530.2	Rabbit	Use with caution
PKC-delta_pS664	PRKCD	Upstate (Millipore)	07-875	932.1	Rabbit	Validated
PKC-pan_BetaII_pS660	PKC	CST	9371	1137.	Rabbit	Validated
PR	PGR	Epitomics	1483-1	549.1	Rabbit	Validated

PRAS40_pT246	AKT1S1	Biosource	441100G	739.1	Rabbit	Validated
PTEN	PTEN	CST	9552	566.3	Rabbit	Validated
Rab11	RAB11A RAB11B	CST	3539	1083.3	Rabbit	Under evaluation
Rab25	RAB25	CST	4314	1150.1	Rabbit	Validated
Rad50	RAD50	Millipore	05-525	987.1	mouse	Validated
Rad51	RAD51	Chem Biotech	na 71	579.3	Mouse	Under evaluation
Raptor	RPTOR	CST	2280	1128.8	Rabbit	Validated
Rb_pS807_S811	RB1	CST	9308	557.9	Rabbit	Validated
RBM15	RBM15	SDI / Novus	21390002	1138.1	Rabbit	Validated
Rictor	RICTOR	CST	2114	1129.4	Rabbit	Use with Caution
Rictor_pT1135	RICTOR	CST	3806	1130.4	Rabbit	Validated
S6_pS235_S236	RPS6	CST	2211	600.8	Rabbit	Validated
S6_pS240_S244	RPS6	CST	2215	601.4	Rabbit	Validated
SCD1	SCD1	Santa Cruz	sc-58420	1127.1	Mouse	Validated
SF2	SFRS1	Invitrogen	32-4500	1131.1	Mouse	Validated
Smad1	SMAD1	Epitomics	1649-1	922.2	Rabbit	Validated
Smad3	SMAD3	Epitomics	1735-1	796.1	Rabbit	Validated
Smad4	SMAD4	Santa Cruz	sc-7966	920.1	Mouse	Validated
Src	SRC	Upstate (Millipore)	05-184	621.2	Mouse	Validated
Src_pY416	SRC	CST	2101	623.18	Rabbit	Use with caution
Src_pY527	SRC	CST	2105	626.5	Rabbit	Validated
STAT3_pY705	STAT3	CST	9131	637.6	Rabbit	Validated
STAT5-alpha	STAT5A	Epitomics	1289-1	638.1	Rabbit	Validated
Stathmin	STMN1	Epitomics	1972-1	718.1	Rabbit	Validated
Syk	SYK	Santa Cruz	sc-1240	1033.1	Mouse	Validated
TAZ	WWTR1	CST	2149	777.1	Rabbit	Validated
TIGAR	C12ORF5	Epitomics	S1711	1107.1	Rabbit	Validated
Transglutaminase	TGM2	Lab Vision	MS-224-P1	908.2	Mouse	Validated
TRFC	TRFC	SDI / Novus	22500002	1140.1	Rabbit	Validated
TSC1	TSC1	CST	4906	1125.1	Rabbit	Use with Caution
TTF1	TTF1	Epitomics	2044-1	1081.1	Rabbit	Validated
Tuberin	TSC2	Epitomics	1613-1	670.30	Rabbit	Validated
Tuberin_pT1462	TSC2	CST	3617	671.2	Rabbit	Validated
VEGFR2	KDR	CST	2479	688.4	Rabbit	Validated
VHL	VHL	BD Biosciences	556347	693.1	Mouse	Use with Caution
XRCC1	XRCC1	CST	2735	906.1	Rabbit	Under evaluation
YAP	YAP1	Santa Cruz	sc-15407	780.3	Rabbit	Under evaluation
YAP_pS127	YAP1	CST	4911	782.1	Rabbit	Under evaluation
YB-1	YBX1	SDI	1725.00.02	700.1	Rabbit	Validated
YB-1_pS102	YBX1	CST	2900	835.1	Rabbit	Validated

Validation Status*

VALID=RPPA and WB correlation > 0.7

Use with Caution=RPPA and WB correlation < 0.7

Under Evaluation=Antibody has given mixed results and / or evaluated by another lab;
we are in the process of (re)validating.

Table S5. Genes with copy number differences ($P < 0.05$) between matched brain metastases ($N=10$) and extracranial metastases ($N=10$)

Number	Gene Symbol	Chromosome	Start	End	Length	Event	Freq. in BM (%)	Freq. in EM (%)
1	ZMYM2	chr13	19430809	19563968	133160	One Copy Gain	0	50
2	GJA3	chr13	19610394	19633183	22790	One Copy Gain	0	50
3	GJB2	chr13	19659603	19665114	5512	One Copy Gain	0	60
4	SAP18	chr13	20612652	20621224	8573	One Copy Gain	0	50
5	SKA3	chr13	20625733	20648741	23009	One Copy Gain	0	50
6	MRP63	chr13	20648371	20651220	2850	One Copy Gain	0	50
7	LINC00539	chr13	20775650	20816998	41349	One Copy Gain	0	50
8	MIPEPP3	chr13	20770263	20865061	94799	One Copy Gain	0	50
9	ZDHHC20	chr13	20844709	20931509	86801	One Copy Gain	0	50
10	MICU2	chr13	20964827	21076355	111529	One Copy Gain	0	50
11	TNFRSF19	chr13	23042508	23148244	105737	One Copy Gain	0	50
12	MIPEP	chr13	23202327	23361587	159261	One Copy Gain	0	50
13	C1QTNF9B-AS1	chr13	23361027	23364242	3216	One Copy Gain	0	50
14	C1QTNF9B	chr13	23363237	23369641	6405	One Copy Gain	0	50
15	ANKRD20A19P	chr13	23379422	23421454	42033	One Copy Gain	0	50
16	SPATA13	chr13	23451764	23779212	327449	One Copy Gain	0	50
17	RNF17	chr13	24236300	24352058	115759	One Copy Gain	0	50
18	CENPJ	chr13	24354411	24395027	40617	One Copy Gain	0	50
19	TPTE2P1	chr13	24400892	24440607	39716	One Copy Gain	0	50
20	PABPC3	chr13	24568275	24570704	2430	One Copy Gain	0	50
21	AMER2	chr13	24633816	24644421	10606	One Copy Gain	0	50
22	MTMR6	chr13	24718340	24759704	41365	One Copy Gain	0	50
23	NUPL1	chr13	24773665	24814561	40897	One Copy Gain	0	50
24	ATP8A2	chr13	24844208	25493420	649213	One Copy Gain	0	50
25	BRCA2	chr13	31787616	31871809	84194	One Copy Gain	0	50
26	N4BP2L1	chr13	31872859	31900315	27457	One Copy Gain	0	50
27	CHRNA7	chr15	30109977	30249676	139700	One Copy Loss	0	50
28	TMCO5B	chr15	31315968	31327048	11081	One Copy Loss	0	50
29	RYR3	chr15	31390468	31945595	555128	One Copy Loss	0	50
30	AVEN	chr15	31945719	32118595	172877	One Copy Loss	0	50
31	CHRM5	chr15	32048380	32144579	96200	One Copy Loss	0	50
32	EMC7	chr15	32163515	32181345	17831	One Copy Loss	0	50
33	PGBD4	chr15	32181565	32183883	2319	One Copy Loss	0	50
34	KATNBL1	chr15	32220166	32289589	69424	One Copy Loss	0	50
35	EMC4	chr15	32304489	32309658	5170	One Copy Loss	0	50
36	SLC12A6	chr15	32309488	32417557	108070	One Copy Loss	0	50
37	NOP10	chr15	32421208	32422654	1447	One Copy Loss	0	50
38	NUTM1	chr15	32422807	32437230	14424	One Copy Loss	0	50
39	LPCAT4	chr15	32438380	32446687	8308	One Copy Loss	0	50
40	GOLGA8A	chr15	32458561	32516959	58399	One Copy Loss	0	50
41	GOLGA8B	chr15	32604775	32663063	58289	One Copy Loss	0	50

Table S6 CNVs in 13 melanoma-related genes in 10 pairs of matched metastases

Patient	CDKN2A		TBX2		PTEN		BRAF		AKT3		MDM4	
	BM	EM	BM	EM	BM	EM	BM	EM	BM	EM	BM	EM
03	Homozygous Copy Loss	One Copy Loss	None	One Copy Gain	Homozygous Copy Loss	One Copy Loss	One Copy Gain	One Copy Gain	One Copy Loss	None	None	None
04	None	None	One Copy Gain	One Copy Gain	None	None	None	None	High Copy Gain	High Copy Gain	High Copy Gain	High Copy Gain
05	One Copy Loss	One Copy Gain	One Copy Gain	One Copy Gain	One Copy Loss	One Copy Loss	High Copy Gain	High Copy Gain	One Copy Gain	One Copy Gain	One Copy Gain	One Copy Gain
09	None	One Copy Gain	One Copy Gain	One Copy Gain	None	None	None	None	None	None	None	None
10	One Copy Loss	None	High Copy Gain	One Copy Gain	One Copy Loss	One Copy Gain	One Copy Gain	One Copy Gain	None	One Copy Gain	One Copy Gain	None
11	One Copy Loss	Homozygous Copy Loss	One Copy Gain	High Copy Gain	One Copy Loss	One Copy Loss	None	None	High Copy Gain	High Copy Gain	High Copy Gain	One Copy Gain
12	One Copy Loss	One Copy Loss	None	None	One Copy Loss	One Copy Loss	High Copy Gain	High Copy Gain	One Copy Loss	None	None	None
13	One Copy Loss	One Copy Loss	One Copy Gain	One Copy Gain	None	None	One Copy Gain	One Copy Gain	None	None	None	None
15	One Copy Loss	One Copy Loss	One Copy Gain	High Copy Gain	One Copy Loss	One Copy Loss	None	One Copy Gain	One Copy Gain	None	None	None
16	None	Homozygous Copy Loss	None	None	One Copy Loss	One Copy Loss	One Copy Gain	One Copy Gain	One Copy Gain	One Copy Gain	One Copy Gain	One Copy Gain

Patient	MYC		MITF		CCND1		MDM2		CDK4		KIT		TERT	
	BM	EM	BM	EM	BM	EM	BM	EM	BM	EM	BM	EM	BM	EM
03	None	None	None	One Copy Gain	High Copy Gain	High Copy Gain	High Copy Gain	High Copy Gain	High Copy Gain	High Copy Gain	High Copy Gain	High Copy Gain	None	None
04	One Copy Gain	One Copy Gain	None	None	None	None	None	None	None	None	None	None	None	None
05	None	None	None	None	None	None	None	None	None	None	None	None	One Copy Gain	None
09	One Copy Gain	One Copy Gain	None	One Copy Gain	High Copy Gain	High Copy Gain	None	None	None	None	None	None	None	None
10	One Copy Gain	None	One Copy Gain	High Copy Gain	None	None	One Copy Loss	None	One Copy Loss	None	One Copy Loss	None	None	None
11	None	None	None	One Copy Gain	One Copy Loss	One Copy Loss	None	None	None	None	None	One Copy Gain	One Copy Loss	Homozygous Copy Loss
12	None	None	One Copy Gain	None	None	None	None	None	None	None	None	None	None	None
13	None	None	None	High Copy Gain	None	None	One Copy Gain	None	None	None	None	None	None	None
15	One Copy Gain	One Copy Gain	One Copy Gain	None	None	One Copy Gain	One Copy Loss	None	One Copy Loss	None	None	None	None	None
16	One Copy Gain	High Copy Gain	None	None	None	None	None	None	None	None	None	None	None	None

BM=brain metastasis

EM=extracranial metastasis

Table S7. Genes differently expressed between six pairs of matched brain and extracranial metastases ($P < 0.01$)

Number	Gene symbol	Linear ratio (BM/EM)	P-value	FDR	Probe ID	Accession
1	LOC100133298	1.75	0.000234	0.422	ILMN_3239361	XM_001719906
2	ANKRD20A1	1.66	0.000237	0.422	ILMN_2215824	NM_032250
3	TMEM119	0.36	0.000271	0.422	ILMN_1738116	NM_181724
4	HRK	0.49	0.00032	0.422	ILMN_2193706	NM_003806
5	CERK	0.64	0.000569	0.422	ILMN_1767475	NM_022766
6	SP100	1.57	0.000751	0.422	ILMN_2390586	NM_001080391
7	THY1	0.6	0.000984	0.422	ILMN_1779875	NM_006288
8	HBA2	8.26	0.001031	0.422	ILMN_2127842	NM_000517
9	LAMA4	1.54	0.001156	0.422	ILMN_1795442	NM_002290
10	TF	8.61	0.001181	0.422	ILMN_1768425	NM_001063
11	SGK3	1.9	0.001213	0.422	ILMN_2366703	NM_170709
12	FAM13B	1.61	0.001339	0.422	ILMN_3258795	NM_001101800
13	HBA2	8.2	0.001416	0.422	ILMN_1667796	NM_000517
14	TSHZ2	0.55	0.001459	0.422	ILMN_1655611	NM_173485
15	MFAP2	0.53	0.001497	0.422	ILMN_1787981	NM_017459
16	FLJ20444	1.52	0.002294	0.422	ILMN_1811181	XM_933028
17	AKAP7	1.96	0.002357	0.422	ILMN_1733690	NM_004842
18	TPP1	1.53	0.002358	0.422	ILMN_1729234	NM_000391
19	BRSK1	1.59	0.002436	0.422	ILMN_2185845	NM_032430
20	PDGFRA	0.52	0.002476	0.422	ILMN_2086470	NM_006206
21	LGI3	1.58	0.002498	0.422	ILMN_1737162	NM_139278
22	EMILIN2	1.73	0.00255	0.422	ILMN_1697268	NM_032048
23	FGFRL1	0.5	0.002794	0.422	ILMN_1795865	NM_021923
24	RN7SK	2.39	0.003064	0.422	ILMN_2074860	NR_001445
25	HBA1	6.53	0.003181	0.422	ILMN_3240144	NM_000558
26	HMOX1	3.54	0.003232	0.422	ILMN_1800512	NM_002133
27	MPZ	1.67	0.003239	0.422	ILMN_1810937	NM_000530
28	ENDOD1	1.55	0.003294	0.422	ILMN_1699022	NM_015036
29	SFRP2	0.38	0.003378	0.422	ILMN_1722898	NM_003013
30	ADORA3	2.33	0.003456	0.422	ILMN_1733259	NM_001081976
31	PHCA	1.51	0.003578	0.422	ILMN_1812552	NM_018367
32	CD68	1.57	0.003843	0.422	ILMN_2359907	NM_001251
33	HERC6	1.83	0.004051	0.422	ILMN_1654639	NM_017912
34	C8orf45	1.57	0.004211	0.422	ILMN_2113738	NM_173518
35	GDF15	1.82	0.004416	0.422	ILMN_2188862	NM_004864
36	PKIA	1.68	0.004483	0.422	ILMN_2337974	NM_181839
37	ADD3	1.71	0.00452	0.422	ILMN_1814526	NM_001121
38	OAS3	2.4	0.004525	0.422	ILMN_1745397	NM_006187
39	CD163	2.53	0.00458	0.422	ILMN_2379599	NM_203416
40	ELOVL2	1.75	0.004922	0.422	ILMN_1716843	NM_017770
41	HBB	7.14	0.004988	0.422	ILMN_2100437	NM_000518
42	SSX1	1.78	0.00499	0.422	ILMN_2247572	NM_005635
43	FGD5	0.59	0.004996	0.422	ILMN_2104141	NM_152536
44	KHDRBS3	1.68	0.005552	0.422	ILMN_1691747	NM_006558
45	OAS1	2.22	0.005594	0.422	ILMN_1675640	NM_001032409

Number	Gene symbol	Linear ratio (BM/EM)	P-value	FDR	Probe ID	Accession
46	DPT	0.47	0.00581	0.422	ILMN_1708107	NM_001937
47	IFIT3	2.85	0.0059	0.422	ILMN_1701789	NM_001031683
48	OAS1	1.81	0.006006	0.422	ILMN_2410826	NM_001032409
49	SGSM2	1.53	0.006012	0.422	ILMN_1779171	NM_014853
50	VSIG4	2.03	0.006083	0.422	ILMN_1669409	NM_007268
51	PROM1	1.59	0.006138	0.422	ILMN_1786720	NM_006017
52	UBA7	1.94	0.006258	0.422	ILMN_1794612	NM_003335
53	VTRNA1-1	1.67	0.006465	0.422	ILMN_3309759	NR_026703
54	LOC644852	1.56	0.006572	0.422	ILMN_1727165	XM_934218
55	SPON1	0.5	0.006647	0.422	ILMN_1791890	NM_006108
56	NAV2	1.79	0.006841	0.422	ILMN_2399300	NM_145117
57	PODN	0.64	0.006874	0.422	ILMN_1770800	NM_153703
58	KHDRBS3	1.7	0.006877	0.422	ILMN_1727790	NM_006558
59	C2orf69	1.6	0.007096	0.422	ILMN_3236377	NM_153689
60	SYNGR1	0.62	0.007125	0.422	ILMN_1721712	NM_145731
61	RARRES2	0.38	0.007134	0.422	ILMN_1810844	NM_002889
62	CILP	0.56	0.00719	0.422	ILMN_2167758	NM_003613
63	PARP10	1.9	0.007313	0.422	ILMN_2262044	NM_032789
64	FLRT3	1.64	0.007521	0.422	ILMN_1805665	NM_198391
65	FLJ44124	1.59	0.007668	0.422	ILMN_2230162	NM_001039755
66	IRF7	2.01	0.008074	0.422	ILMN_1798181	NM_004029
67	SYNGR1	0.59	0.008342	0.422	ILMN_1810875	NM_004711
68	KIAA1751	1.57	0.008459	0.422	ILMN_2415979	NM_001080484
69	NQO1	2.01	0.008558	0.422	ILMN_1720282	NM_000903
70	STARD8	1.65	0.008598	0.422	ILMN_1799600	NM_014725
71	BIRC3	1.61	0.008701	0.422	ILMN_2405684	NM_182962
72	LOC100129211	1.52	0.008725	0.422	ILMN_3238053	XM_001718981
73	TXNIP	2.65	0.008983	0.422	ILMN_1697448	NM_006472
74	DMC1	1.55	0.008989	0.422	ILMN_2162367	NM_007068
75	CILP	0.34	0.009093	0.422	ILMN_1723847	NM_003613
76	FKBP4	0.65	0.009112	0.422	ILMN_1782045	NM_002014
77	RN7SK	4.98	0.009259	0.422	ILMN_1739423	NR_001445
78	SULT1A1	1.57	0.009366	0.422	ILMN_2404795	NM_177530
79	LMOD3	1.58	0.009674	0.422	ILMN_1785703	NM_198271
80	ERP27	2.01	0.00969	0.422	ILMN_1655261	NM_152321
81	DEF8	0.65	0.009763	0.422	ILMN_1656185	NM_017702
82	PHLDA3	1.84	0.009763	0.422	ILMN_1659106	NM_012396
83	ITM2A	1.5	0.009765	0.422	ILMN_2076600	NM_004867
84	GLDN	1.56	0.009903	0.422	ILMN_1704376	NM_181789
85	XAF1	2.34	0.00994	0.422	ILMN_2370573	NM_199139
86	MFAP5	0.46	0.009983	0.422	ILMN_1733415	NM_003480

BM=brain metastasis, EM=extracranial metastasis

Linear ratio: calculated by dividing the mean expression of BM with the mean expression of EM

FDR: false discovery rate estimated by random permutation ($N=10,000$)