**Supplemental Methods**

**Cell culture.** All cells were cultured in a humidified incubator with 5% CO2 at 37 °C. RPMI1640 medium supplemented with 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM L-glutamine and 10 % fetal bovine serum was used to grow all human and murine melanoma cell lines. Lenti- and retrovirus production was performed in HEK 293T cells, cultured in DMEM medium supplemented with 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM L-glutamine and 10 % fetal bovine serum (all media reagents were purchased from Life Technologies). All cells were negative for mycoplasma as tested on a monthly basis. None of the cell lines used in this study is listed in the current ICLAC database (v8.0) of cross-contaminated or misidentified cell lines. For cytokine stimulation experiments cells were treated with TNFα at 1000 U/ml and HGF at 50 ng/ml (both Peprotech, Germany). For inhibitor treatment cells were cultured in medium containing 50 nM trametinib (MEKi), 100 nM SCH-772984 (EKRi), 1 µM BEZ235 (Pi3Ki/mTORi) or 1 µM MK-2206 (AKTi), all from Selleckchem (Distributor Absource, Germany) and stocks dissolved in DMSO.5-Azacytidine (Sigma) was dissolved at 10mM in DMSO and stored at -80°C up to six month. Cells were treated daily with 5 µM 5-azacytidine for 6 days. Afterwards medium was changed for stimulation containing 5 µM 5-Azacytidine, TNF-α (1000 U/ml) and HGF (50 ng/ml) for three more days.

**Flow cytometry (FACS) analysis.** Cells were trypsinated from culture wells with 0.05% trypsin and resuspended in FACS buffer (PBS, 5% FCS). For human cells 2x105 cells were stained 30min on ice in 50µl FACS buffer, Brilliant Violet 421™ anti-CD73mAb 1:100 (clone AD2, Biolegend). Propidium Iodide staining (BD Bioscience) was included for cells treated with 5-azacytidine. For murine cells 2x105 cells were stained as described using biotin anti-mouse CD73 mAb 1:200 (clone TY/11.8, Biolegend) and biotin rat IgG1κ isotype control 1:200 (Biolegend), respectively. Brilliant Violet 421™ streptavidin (Biolegend) was used for detection at a final concentration of 300 ng/ml. Twenty thousand events in the P1 living cell gate were recorded on a FACS Canto II flow cytometer (BD Bioscience) and analyzed with FlowJo software (TreeStar, V7.8 for Mac).

**Mice.** C57BL/6 mice (H-2b) were purchased from Charles River. TCR-transgenic Pmel-1 mice expressing an αβ TCR specific for amino acids 25–33 of human and mouse gp100 presented by H2-Db were bred as described previously (1). All animal experiments were approved by the local government authorities (LANUV, NRW, Germany) and were performed according to the institutional and national guidelines for the care and use of laboratory animals.

**HCmel3 inoculation.** HCmel3 and HCmel3-R late relapse cell lines were established and characterized as described in our previous studies (1,2). Groups of syngeneic age and sex matched C57BL/6 mice were injected intracutaneously with 4 × 105 HCmel3 cells into the flanks. Non-treated mice were killed when tumors reached a size of >10 mm in diameter. ACT therapy was started (for protocol see below) when HCmel3 melanomas reached a size between 6-8 mm in diameter. For early-during-treatment samples mice were killed between 12 and 20 days after the start of Pmel-1 ACT treatment. Experiments (NT and EDT) were performed in groups of five mice and repeated twice. Late relapse melanoma samples and the therapeutic course have been described previously (1).

**Adoptive T-cell transfer protocol.** ACT was carried out according to the ‘CLVI’ protocol as previously described (1). Preconditioning of mice was achieved by a single intraperitoneal injection of 2 mg cyclophosphamide 1 day before intravenous injection of 2 × 106 naive gp100-specific CTLs isolated from spleens of TCR-transgenic Pmel-1 mice. Pmel-1 T cells were activated in vivo by one intraperitoneal injection of 5 × 108 plaque-forming units of the recombinant adenoviral vector Ad-gp100. Fifty micrograms of CpG 1826 (MWG Biotech) and 50 μg of poly(I:C) (Invivogen) in 100 μl PBS were injected peritumorally after 3, 7 and 10 days. Ad-gp100 was propagated on HEK 293 cells, purified by caesium chloride density-gradient centrifugation and subsequent dialysis according to standard protocols.

**Human primary melanomas (Bonn cohort)**. Patient samples and clinical data were obtained with the approval of institutional Ethics Committee boards and patients’ consents at the Skin Cancer Centre of the University Hospital Bonn, Germany. We retrospectively studied 70 cutaneous metastases and 126 primary cutaneous melanomas from patients, who were diagnosed in the Department of Dermatology at the University Hospital Bonn between January 1st 2000 and December 31th 2010 and underwent wide local excision of their primary tumor and sentinel lymph node biopsy. At least one representative H&E stained slide from each melanoma sample was assessed for Breslow thickness, histological subtype and ulceration by two observers, without knowledge of patient outcome.

**Histology and immunohistology (CD73).** The following protocols were used for immunohistochemistry of mouse melanomas and human melanomas from Bonn (Germany) and UCLA (USA). Human melanomas from the Sydney cohort were stained with a different protocol (see below). Mouse tissue samples were immersed in a zinc-based fixative (BD Pharmingen) and human melanoma samples in buffered paraformaldehyde (DAKO). Tissues were embedded in paraffin and sections stained with H&E according to standard protocols. Immunohistochemistry for human melanoma specimens was performed with a polyclonal rabbit-anti human CD73 antibody (Sigma HPA017357, 1:600, antigen-retrieval pH6 10 min), rabbit anti-human CD14 mAB (Clone EPR3652, LifeSpan Bio Sciences, dilution: 1:25). Immunohistochemistry for mouse tissue specimens was performed with rabbit-anti- CD73 mAB (clone D7F9A, #13160 Cell signaling, dilution 1:300, antigen-retrieval pH6 10 min, mouse and human reactive). Incubation with the primary antibodies was followed by incubation with enzyme-conjugated secondary antibodies and the LSAB-2 color development system (DAKO). Heavily pigmented mouse melanomas were bleached before staining (20 min at 37°C in 30% H2O2 and 0.5% KOH, 20 sec in 1% acetic acid and 5 min in TRIS buffer). Stained sections were examined with a Leica DMLB immunofluorescence microscope. Images were acquired with a JVC digital camera KY-75FU and processed with Adobe Photoshop. A semi-quantitative scoring systems (0 = no expression, 1 = low, 2 = intermediate, 3 = high) has been applied for CD73 expression intensity on melanoma cells.

**Bonn patient cohort/Treatments.** Patients were diagnosed with primary or metastatic melanoma between January 1st 2000 and December 31th 2010. Dacarbazine was the only approved systemic treatment for metastatic melanoma till 2011 at our institution (Department of Dermatology, University Hospital Bonn). Patients with primary melanomas underwent surgical resection, which was largely curative. 19/126 of these patients had recurrent disease and received best supportive care or dacarbazine before death. One additional patient with recurrent disease was treated with a BRAF inhibitor. Four of the patients with cutaneous melanoma metastases were treated with an immune-checkpoint-inhibitor (ipilimumab, nivolumab, pembrolizumab).

**UCLA patient cohort.** Patients characteristics, treatment with pembrolizumab and sample collection have been previously described and approved (3). Patients in the study underwent biopsy of a metastatic tumor within 30 days after treatment onset and one or more optional biopsies at later times points. Samples were immediately fixed in formalin followed by paraffin embedding. Biopsy collection and IHC analyses were approved by UCLA IRBs 11-001918 and 11-003066 (3). The MART-1 ACT trial and material collection was also previously described (4).

**Sydney patient cohort.** The study was undertaken with Human Ethics Review Committee approval and patient's informed consent (Protocol No X10-0305 & HREC/10/RPAH/539). Patients eligible for study had unresectable AJCC stage III or stage IV melanoma. 21 archival tumor samples were retrieved from 8 patients with metastatic melanoma who were treated with anti-PD-1 immunotherapy (Nivolumab n =2, Pembrolizumab n = 6) between 2011 and 2016. Patients with BRAF V600E mutations (n = 3) were previously treated with combination BRAF and MEK inhibitor therapy. Pre-immunotherapy treatment (PRE) and progression (PROG) samples were identified for each patient.

**CD73 immunohistochemistry (Sydney cohort).** For human CD73 staining, tissue sections were cut at 3μm onto superfrost+ glass slides and stored at 4°C until IHC was performed. IHC was performed on a Dako autostainer/PT-Link system using a high pH target retrieval buffer (Dako, K8005) as per the manufacturer's instructions. The primary antibody against CD73 (clone D7F9A Rabbit mAb;CST#13160) was incubated for 45 min at room temperature at a 1:200 dilution and visualized using the MACH3 Rabbit HRP polymer detection system (Biocare; M3R531) and DAB Chromogen Kit (Biocare; BDB2004) as per the manufacturer's instructions. Immunohistochemistry was evaluated on tissue microarray cores by assigning a score based on tumor cell CD73 immunostaining as follows; negative (0), weakly cytoplasmic no evidence of membrane staining (1), incomplete membrane staining (2), strong complete membrane staining (3). For whole tissue section CD73 immunostaining a score for the intensity of tumor CD73 staining was assigned as above and then multiplied by the percentage area of CD73 positive tumor cells across the entire specimen.

**RNA isolation and quantitative real time PCR analysis.** 0.2-2x106 cells were directly lysed in culture wells by RLT buffer (Qiagen) and frozen at -80°C. Lysates were mixed at equal volumes with 70% ethanol and RNA isolation was performed using Zymo-Spin™ II Columns (Zymo Research) including buffer RW1 (Qiagen) and Zymo RNA Wash Buffer (Zymo Research) washing steps according to the manufacturer’s instructions. RNA was eluted in 15-40 µl distilled aqua ad iniectabilia (Ampuwa®) and concentration measured at a NanoDrop2000 (ThermoFisher). 300-1000 ng total RNA was used in a 10 µl cDNA synthesis reaction according to the protocol of the All-in-One cDNA synthesis Supermix (Biotool) and incubated 10 min at 25°C, 30 min at 42°C and 5 min at 85°C.One microliter of 1:4 diluted cDNA per probe was mixed with 9 µl Fast EvaGreen® qPCR Mix II (ROX) (BioBudget) and analyzed in quantitative realtime PCR (qPCR) in technical duplicates at a LightCycler®480 system (Roche). For quantification of expression standard-curve based primer efficiency tests were incorporated in each run and expression was normalized to the housekeeping gene Ubiquitin.

**Vector cloning and viral transduction.** For retrovirus generation HEK293T cells were transfected with the retroviral expression plasmids using calcium phosphate and the packaging plasmids gag-pol and pCMV-VSVG. For lentivirus generation from lentiviral expression plasmids second-generation packaging constructs pCMVdelta8.91 and pCMV-VSVG were used. Medium was replaced 16 h after transfection and viral supernatant was collected after 24 more hours, filtered through 0.45 µm pore syringe filters and incubated for 24 h with target cells. Collection medium was renewed on viral particle producing HEK293T cells for another 24 h and a second round of infection of target cells was performed.Antibiotic selection was initiated 48 h after second infection of target cells using blasticidine at a concentration of 10 µg/ml and puromycin at 2 µg/ml (both Sigma Aldrich) and carried out till none-infected control cells had been killed completely for approximately 4 days. For generation of c-Jun-citrine- and citrine- inducible constructs the transactivator pRp-rtTA (2) was used and c-Jun-citrine/ citrine amplified from pRp-c-Jun-citrine (2) and cloned into the tet-inducible lentivirus pLV-tetO (kindly provided by Jochen Uttikal, Deutsches Krebsforschungszentrum, Heidelberg, Germany) via SalI and MluI sites.

**Immunoblot analysis.** Cells were lysed at 2,000 cells/µl Laemmli buffer and heated at 95°C for 5 min.10% SDS-polyacrylamide gel electrophoresis gels were loaded with 6 µl Broad Range Marker (Santa Cruz sc-2361) and 15 µl lysate per lane and run 10 min 100 V, 1.5 h 140V. Wet blotting to nitrocellulose membrane (0.2 µm pore size; GE Healthcare) was performed for 1.5 h at 450 mA. Membranes were blocked in 5% BSA in TBS with 0.5% Tween (TBS-T) for 1 h at room temperature. Primary antibodies were incubated in 5% BSA in TBS-T over night at 4°C. Antibodies used: mouse anti-mouse/human-AKT (clone 40D4, cs#2920, Cell Signaling, 1:2000), mouse anti-mouse/human-β-Actin (clone C4, sc-47778 Santa Cruz, 1:1,000), rabbit anti-mouse/human-CD73 (clone D7F9A, cs#13160 Cell Signaling, 1:1000), rabbit anti-mouse/human-c-Fos (clone 9F6, cs#2250, Cell Signaling, 1:1000), rabbit anti-mouse/human-c-Jun (clone 60A8, cs#9165 Cell Signaling, 1:250), rabbit anti-mouse/human-ERK1/2 (cs#9102 Cell Signaling, 1:1000), rabbit anti-mouse/human-FOSL1 (polyclonal, sc-183, Santa Cruz, 1:200), mouse anti-GFP (clone B2, sc-9996, Santa Cruz, 1:200), mouse anti-mouse/human-IκBα (clone L35A5, cs#4814, Cell Signaling, 1:1000), rabbit anti-human-MITF (polyclonal, HPA003259, Atlas Antibodies, 1:250), rabbit anti-mouse/human-p-AKT (clone D9E, cs#4060, Cell Signaling, 1:2000), rabbit anti-mouse/human-p-c-MET (clone D26, cs#3077, Cell Signaling, 1:1000), mouse anti-mouse/human-p-ERK1/2 (clone E-4, sc-7383 Santa Cruz, 1:200), rabbit anti-mouse/human-TRP2/tyrosinase (polyclonal, PEP-8, provided by V. Hearing). Infrared fluorescent secondary antibodies IRDye® 680LT and 800CW from LI-COR for protein detection were added at 66.7ng/ml for 1 h at room temperature in 5% BSA in TBS-T. Blots were scanned on an Odyssey Sa Imaging System.

**Chromatin Immunoprecipitation (ChIP) and ChIP-quantitative PCR.** MaMel.79b cells with inducible c-Jun-Citrine or inducible citrine were expanded to 80% confluency on three 15 cm culture dishes per cell line. c-Jun-citrine/citrine was induced for 24h by changing medium to 25 ng/ml doxycycline. Cells were harvested and processed for Chromatin Immunoprecipitation using SimpleChIP® Enzymatic Chromatin IP Kit (cs#9003, Cell Signaling) as indicated by the manufacturers protocol. For optimal Chromatin Digestion the amount of Micrococcal Nuclease was titrated to 2000 gel units/ 15 cm dish. Sonification was done on ice 3 times 20 seconds at a Branson Analog Sonifier 250 set on 20% output, 20% duty cycle. Quality of chromatin preparation was controlled by ethidium bromide 1% agarose gel electrophoresis. Per IP 10 µg of chromatin preparation was used. Kits containing control antibodies were used as suggested, c-Jun-citrine/ citrine was precipitated using 25 µl GFPTrap®-MA (Chromotek) per IP and incubated 4 h at 4°C. Each IP was eluted in 50 µl volume. For quantitative PCR technical duplicates were measured using 1 µl chromatin elution per reaction. For every primer pair efficiency was monitored by standard dilutions of the input controls. Primer sequences used are listed in **Table S8**.

**Genomic DNA isolation and bisulfite conversion of DNA.** 2-5x106 cells were resuspended in 500 µl lysis buffer (100 mM Tris.HCl pH8.0, 5 mM EDTA pH8.0, 0.2% SDS, 200 mM NaCl, 100 µg/ml proteinase K) and incubated at 56°C over night. 166.7 µl 5 M NaCl was added and genomic DNA was precipitated by addition of 2 volumes ethanol. Precipitated genomic DNA was transferred to new reaction tubes, pelleted, washed in 70% ethanol, dried and dissolved in 50 µl water. For bisulfite conversion of 500 ng of genomic DNA the EZ DNA-Methylation Direct Kit (Zymo Research) was used according to the manufacturer’s instructions. Converted DNA was eluted in a volume of 10 µl.

**Dual barcoding PCRs for deep sequencing on bisulfite converted DNA.** First level PCR was run in a volume of 25 µl using DreamTaq Polymerase (Thermo Scientific) and 1 µl bisulfite converted DNA template. Annealing at 54°C, elongation 40 sec, 20 cycles. Primers used for first level PCR are listed in **Table S8**. 2 µl of first level PCR was transferred to second level barcoding PCR in a volume of 25 µl using Phusion Polymerase (Thermo Scientific), annealing at 60°C, elongation 40 sec, 20 cycles and primers for barcoding samples for deep sequencing analysis (primer sequences see **Table S8**).

**sgRNA cloning.** Single guide RNAs (sgRNAs) were designed to span the AP-1-sites in the *NT5E (CD73)* first intron obeying design rules described by http://www.genome-engineering.org. AP-1-sites were chosen to match the sites amplified in ChIP qPCR analysis. For targeting *NT5E (CD73)* with high specificity a double-nicking approach was chosen and a sgRNA pair in exon 1 was designed with a +5 bp sgRNA offset, creating 39 bp 5’ overhangs according to the design rules described by Ran *et. al* (5). A list of sgRNA sequences used is provided in **Table S8**. For CRISPR-Cas9 plasmid cloning complementary oligonucleotides containing sgRNA sequences and BbsI restriction site overhangs were purchased from Microsynth and dissolved at 3mg/ml. Oligoannealing was carried out by mixing 1 µl of each oligo in 48 µl annealing buffer (100 mM NaCl, 50 mM HEPES, pH 7.4) and incubating at 95°C 4 min, 70°C 10 min, 70°C 1 min 30 sec, decreasing 1°C per cycle for total 60 cycles. Vector px330-U6-Chimeric\_BB-CBh-hSpCas9 (px330) was BbsI digested and gel purified. The px330 plasmid was obtained from Addgene (#42230). Annealed oligos were ligated in px330 and transformed into DH10B competent *e.coli.* Single clones were picked and validated by Sanger sequencing using primer px330-U6-start: 5’-gagggcctatttcccatgattc-3’ at MicroSynth AG (Switzerland).

**Generation of polyclonal CD73 intronic enhancer CRISPR-Cas9 targeted cell lines.** MaMel.79b inducible c-Jun-citrine were co-transfected with prp-mTomato and px330-sgRNA plasmids (ratio 1:3), SK-MEL28 was co-transfected with prp-GFP and px330-sgRNA plasmids (ratio 1:3) using Fugene® HD transfection reagent according to manufacturer's instructions. Cells were FACS sorted 48 h post transfection on prp-mTomato/GFP fluorescent cells and expanded in culture.

**Generation of polyclonal CD73 knockout cell lines by CRISPR-Cas9 double nicking.** Left (R3) and right (L3) sgRNAs targeting CD73 were amplified from 10 ng of the respective px330-sgRNA plasmids in a 50 µl reaction using a mix of Phusion/ Dreamtaq polymerase (Thermo Scientific) in 35 cycles (annealing 60°C, elongation 1 min). Primers: px330-U6-start and px330-gRNA-rev1 are listed in **Table S8**. PCR products were size-separated by ethidium bromide 1% agarose gel electrophoresis. 435 bp (R3/ L3) PCR product bands were cut out and purified using the column-based InnuPrep gel extraction kit (Jena Analytik) according to the manufacturer’s protocol.MaMel.102 and MaMel.65 were co-transfected with vector px461-pSpCas9n(BB)-2A-GFP (px461) (Addgene plasmid #48140)and both px330-sgRNA-PCR-products (ratio 6:1:1) and FACS sorted on GFP positive cells 48 h post transfection. In order to increase knockout frequency polyclonal CD73 knockout cell lines were FACS sorted on the CD73 negative cell population 3 weeks after gRNA transfection. Knockout frequency was analyzed by deep sequencing.

**Cell sorting of polyclonal CD73 intronic enhancer CRISPR-Cas9 targeted cell lines.** For sorting CD73low and CD73high subfractions MaMel.79b inducible cJun -citrine derived cell lines were cultured for 5 days in the presence of 25 ng/ml doxycycline. Cells were harvested by trypsinization and stained for CD73 as described above. MaMel.79b inducible c-Jun-citrine: 10,000 cells of each 10% most dim, 10% brightest and total CD73 positive fraction were sorted at a BD Influx™ cell sorter into 2x lysis buffer (0.4  mg per ml proteinase K, 2  mM CaCl2, 6  mM MgCl2, 2  mM EDTA, 2% Triton X-100 and 20  mM Tris pH 7.5), incubated at 65°C 1 h, 95°C 15 min, and total lysate volume was used for dual barcoding PCRs for NGS. SK-MEL28: 100,000 cells were sorted as described above. Prior to lysis cells were pelleted and resuspended in 20 µl 1x lysis buffer and incubated as annotated above. Dual barcoding PCRs for NGS were run in technical triplicates.

**Dual barcoding PCRs for deep sequencing on CRISPR-Cas9 targeted cell lines.** First level PCR was run in a volume of 25 µl using Phusion polymerase (Thermo Scientific) and 4 µl DNA lysate, annealing at 60°C, elongation 30sec, 19cycles. Primers used are listed in **Table S8**. Two microliters of first level PCR was transferred to second level barcoding PCR in a volume of 12.5 µl using the same cycling conditions and primers for barcoding samples for deep sequencing analysis (primer sequences see **Table S8**).

**Deep sequencing.** PCR products were pooled and size-separated using a 1.5 % agarose gel run at 100 V. After visualization with ethidium bromide under UV light, DNA bands from 350 to 450  bp were cut out and purified using Jena Analytik innuPrep gel extraction kit according to the manufacturer’s protocol. Eluted DNA was precipitated by adding 0.1 volumes of 3 M NaOAc (pH 5.2) and 1.1 volumes of isopropanol. After centrifugation for 15 min at 4 °C, the resulting pellets were washed once in 70% EtOH and air-dried. Thirty microliters of water was added, non-soluble fractions were spun down and removed, and the DNA concentration was quantified using a NanoDrop spectrophotometer system. DNA input for 10,000 reads per sample was calculated. DNA was diluted and deep sequencing was performed according to the manufacturer’s protocol using the MiSeq (Illumina) bench top sequencing system. Data were obtained in FASTQ format.

**Evaluation of deep sequencing data.** Raw deep sequencing reads of CRISPR-Cas9-targeting/ FACS sorting experiments were analyzed using the web tool Outknocker.org analysis software (6). AP-1-site sequences within the respective sgRNAs were set as nuclease target site for analysis for c-JUN/AP-1-site editing, allowing OutKnocker to output the number of amplicon reads that contains indels overlapping with the AP-1 consensus sequence. For ctrl site targeting whole sgRNA target site was used for target site analysis. Targeted allele frequencies were calculated by the ratio of reads containing indels at the target site to total reads aligned to the reference sequence. To compensate for individual sgRNA editing efficiencies, editing frequencies of the individual sgRNAs in CD73high and CD73low sorted fractions were normalized to the editing frequencies of the CD73total populations. For analysis of CpG island methylation using bisulfite conversion based deep sequencing raw deep sequencing reads were aligned to the reference amplicon sequence while ignoring any cytidine bases. Successfully aligned reads were aggregated to calculate the base frequencies at given amplicon positions. The methylation frequency of an individual CpG motif was calculated as the ratio of unconverted C bases to the sum of C and T bases that were sequenced at a specific position.

**BROAD melanoma cell line panel.** Raw CEL files (Affymetrix platform) of 88 melanoma cell lines (7) were downloaded from the BROAD melanoma portal (https://www.broadinstitute.org/software/cprg/?q=node/46) and normalized by robust multichip average (RMA) using the affy package and log2-transformed as previously described (2). Verfaillie 'proliferative' and 'invasive' phenotype signature genes were obtained from the original publication (8). The TNF response signature was previously described by us (2). Gene signature expression was calculated by averaging log2 expression values of signature genes. Gene probes with the highest signal intensity were selected and redundant gene probes were removed. Used affy gene probes: *NT5E*, 203939\_at; *MITF*, 207233\_s\_at; *WNT5A,* 205990\_s\_at; *AXL*, 202686\_s\_at. Moving average plots have been previously described and R source code is available in the original publication (2).

**Microarray analysis of gene expression.** Mouse melanomas were collected and immediately snap frozen in liquid nitrogen. Total RNA was isolated using TRI Reagent (Sigma-Aldrich) and purified using RNA-isolation columns. RNA was quantified fluorimetrically and assayed for integrity with the Agilent Bioanalyzer (Agilent Technologies). One hundred nanogram of RNA was converted to biotinylated cRNA using one round of amplification with the Illumina Labelling Kit (Illumina) and one round of T7 polymerase amplification and hybridized to Illumina Murine Beadchips WG6 v. 2.0. After hybridization and staining, the arrays were scanned in an Illumina Bead Station, and the images processed using Illumina Bead Studio software. Raw microarray data was extracted from the Illumina BeadStudio software and imported into the R statistical programming environment and the Bioconductor platform using the beadarray package (9). Variance stabilization (vsn2) and normalization were performed followed by quality assessment of the fit (10). Expression data was log2 transformed for further analyses.

**Gene set enrichment analysis (GSEA)**. GSEA was performed using the BROAD javaGSEA standalone version (http://www.broadinstitute.org/gsea/downloads.jsp) and the gene set collections of the BROAD molecular signature database (MSigDbv5, http://www.broadinstitute.org/gsea/msigdb/index.jsp) as described (2,11). We used the default setting of 1000 permutations and the gene-set permutation mode. Gene probe identifiers were collapsed to symbols prior to the analysis using the respective annotation files for affymetrix or illumina beadarray expression platforms. The probe 203939\_at representing *NT5E* was used for Pearson correlation analysis in human MITFhigh melanoma cell lines. For GSEA of group comparisons we used the eBayes moderated t-test statistics from the limma package (12) for differential gene expression analysis as metric for the pre-ranked gene list algorithm. Gene expression data of Braf*V600E*xCdk4R24C mouse melanomas have been previously deposited to the GEO archive with the accession number GSE71879 (13). Gene expression data of non-treated (NT) and late relapse (R) HCmel3 melanomas have been previously deposited to the GEO archive with the accession number GSE40213. Gene expression data of additional non-treated (NT) and early during treatment (EDT) HCmel3 melanomas will are available through GSE99925.

**Statistical tests**. Statistical tests were performed with the R-computing platform, MS excel or Prism graphpad. We specify within the manuscript or legends the name (t-test, wilcoxon test) of the test and its direction (one-sided or two-sided). If applicable we also performed corrections for multiple comparison, e.g. the Benjamini & Hochberg method (B&H), which is also referred to as false-discovery rate (FDR).

**References to Supplemental Experimental Procedures**

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