SUPPLEMENTARY INFORMATION

Phenformin enhances the efficacy of ERK inhibition in NF1-mutant melanoma

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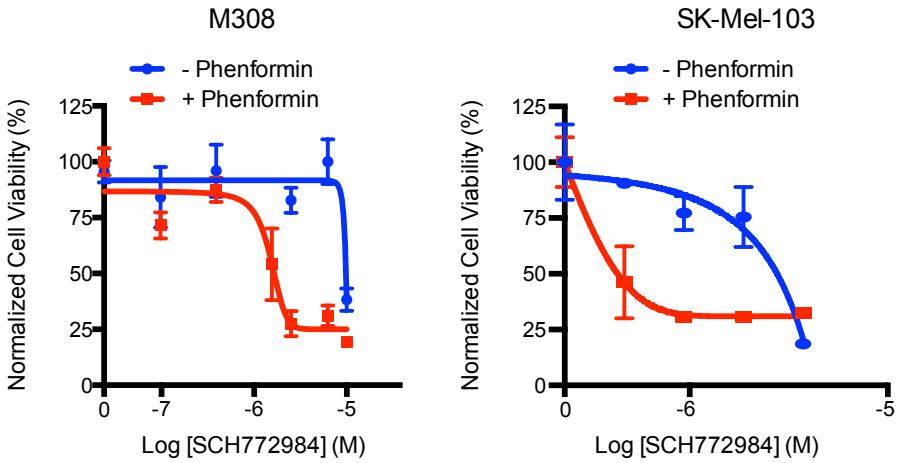
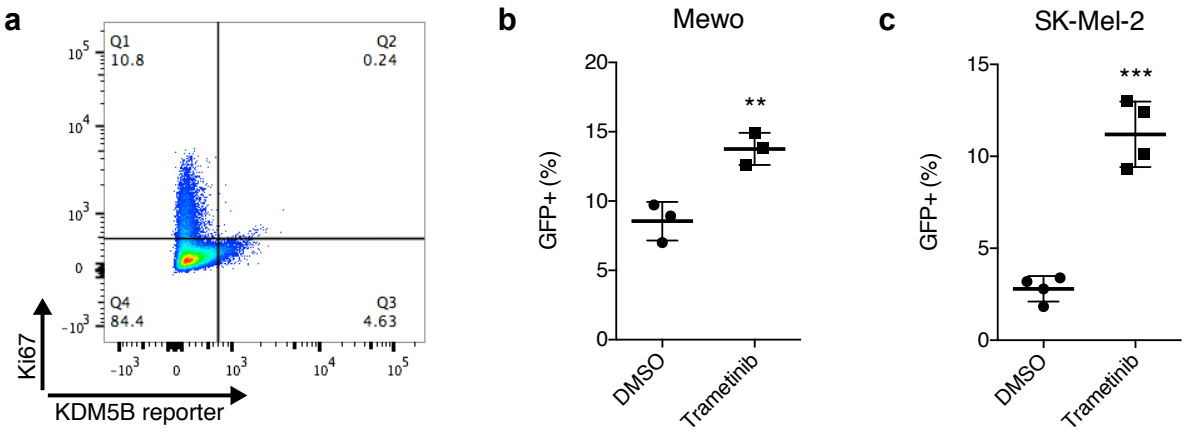
Supplementary Table S1: NF1, BRAF and NRAS mutation status of cell lines, as published by Nissan *et al.,* 2014 or the Cancer Cell Line Encyclopedia (Barretina *et al.,* 2012).

Cell line	NF1	BRAF	NRAS
LOXIMVI	Q1174*	V600E, I208V	WT
Mewo	Q1336*, heterozygous NF1 deletion	WT	WT
M308	Q1070*	V600E	WT
SK-Mel-103	Focal NF1 deletion	WT	Q61R
SK-Mel-113	homozygous deletion	WT	WT
SK-Mel-217	focal intragenic NF1 deletion	WT	WT
WM88	R1306Q	V600E	WT
WM3918	focal intragenic NF1 deletion	-	-



Supplementary Figure S1: M308 and SK-Mel-103 cells were treated with varying concentrations of ERKi SCH772984 alone or in combination with 0.25 mM (M308) or 0.1 mM (SK-Mel-103) phenformin. After 72-hour drug treatment, cell proliferation was assessed by DNA-based CyQUANT assay. Cell number was normalized to no drug treatment.



Supplementary Figure S2: KDM5B-positive cells are slow-cycling and KDM5B expression is induced by MEK inhibition in NF1-mutant and NRAS-mutant melanoma. (**a**) WM115 cells stably expressing the KDM5B reporter construct were stained with proliferation marker Ki67 and subjected to FACS analysis. (**b-c**) Mewo (NF1-mutant) and SK-Mel-2 (NRAS mutant) cells were treated with MEKi trametinib (1 and 0.1 μM for Mewo and SK-Mel-2, respectively) for 72 hours and distribution of KDM5B (GFP)-positive cells analyzed by FACS.