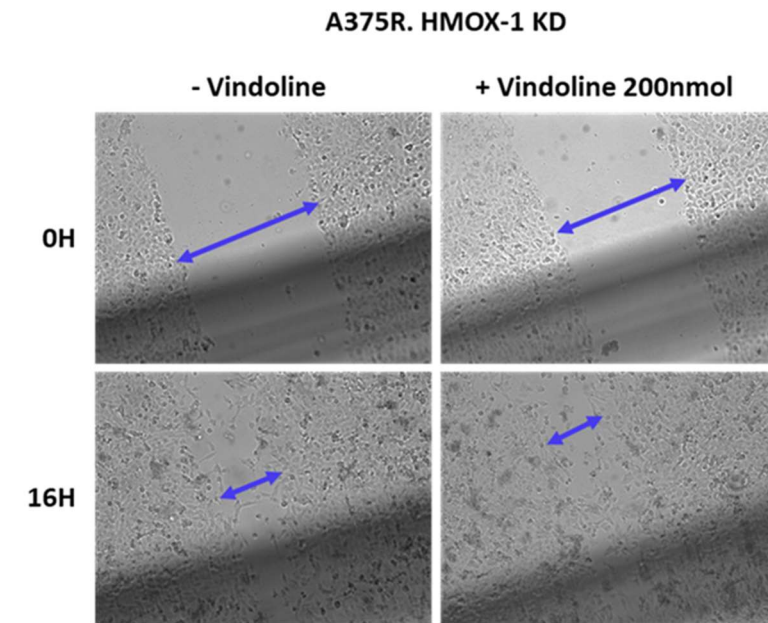
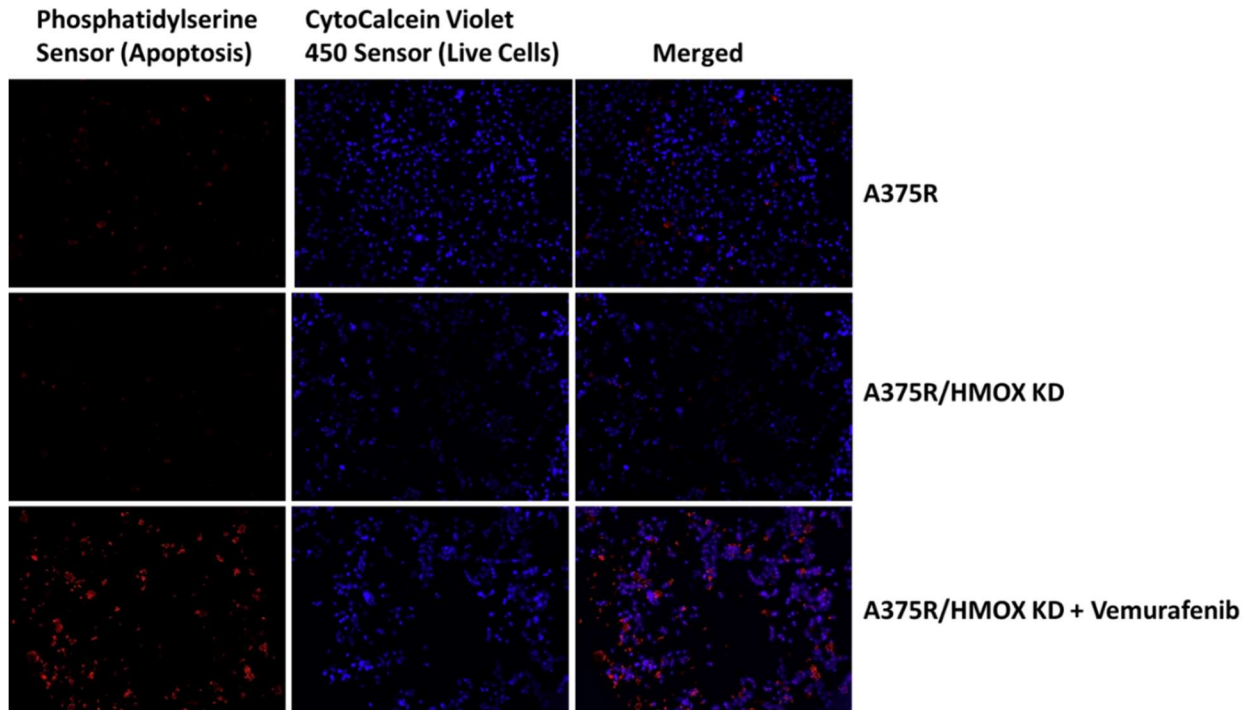


## Supplementary materials



**Figure S1.** Cell migration was evaluated by using wound healing assay in presence or absence of an anti-mitotic agent. No difference was observed before and after Vindoline treatment. No contribution of cell division to the increase of the cell population in the denuded space.



**Figure S2.** Measurement of apoptosis in A375R and A375R/HMOX-1 KD cell exposed to vemurafenib treatment. HMOX knock down (KD) does not initiate apoptosis before vemurafenib treatment.

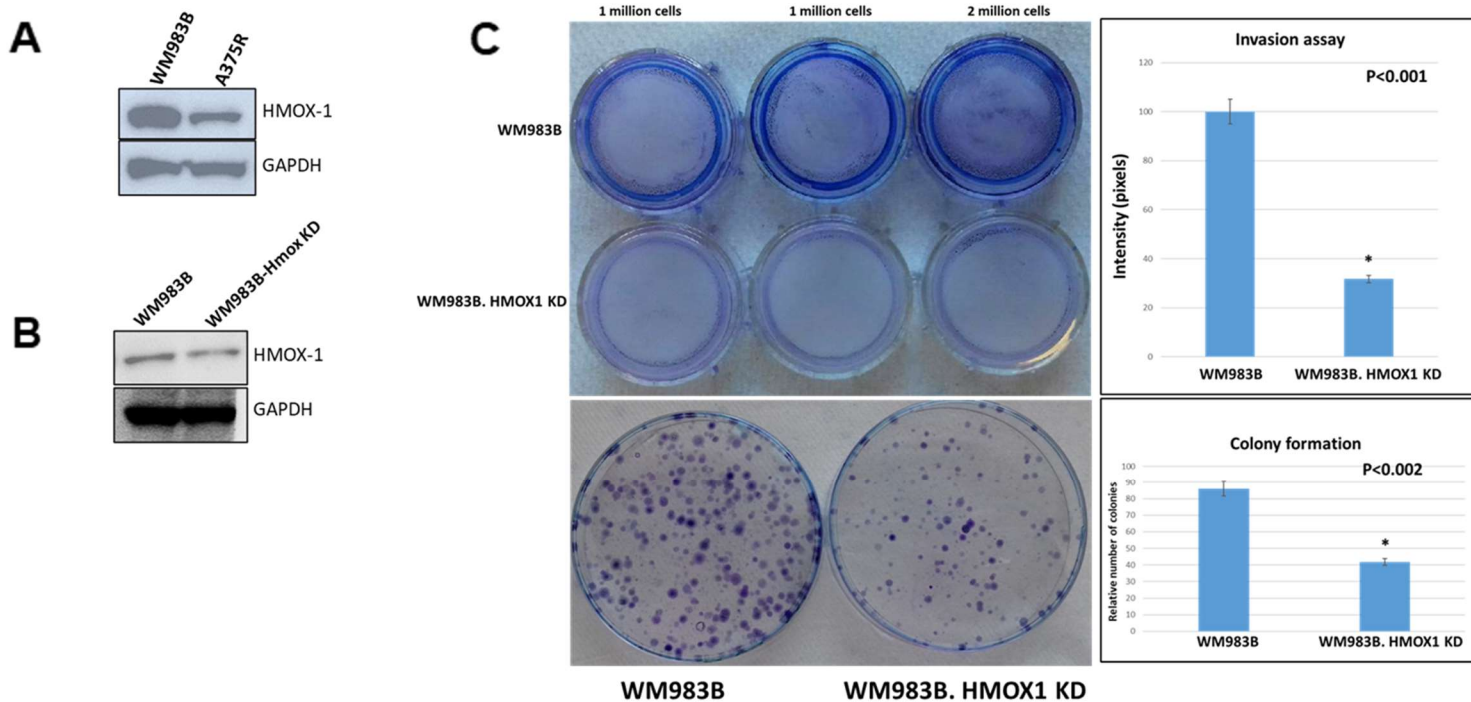
		HMOX-1	BRAFV600E
Primary malignant melanoma	#Cores	15	15
	Cytosolic (%)	13 (86.7)	14 (93.3)
	Nuclear (%)	3 (20)	5 (33.3)
Metastatic malignant melanoma	#Cores	15	15
	Cytosolic (%)	13 (86.7)	15 (100)
	Nuclear (%)	6 (40)	5 (33.3)

**Figure S3.** Localization of BRAF<sup>V600E</sup> and HMOX-1 in human melanoma cores. Table summarizing the number of samples with cytoplasmic or nuclear BRAF<sup>V600E</sup>/HMOX-1 after IHC analysis.

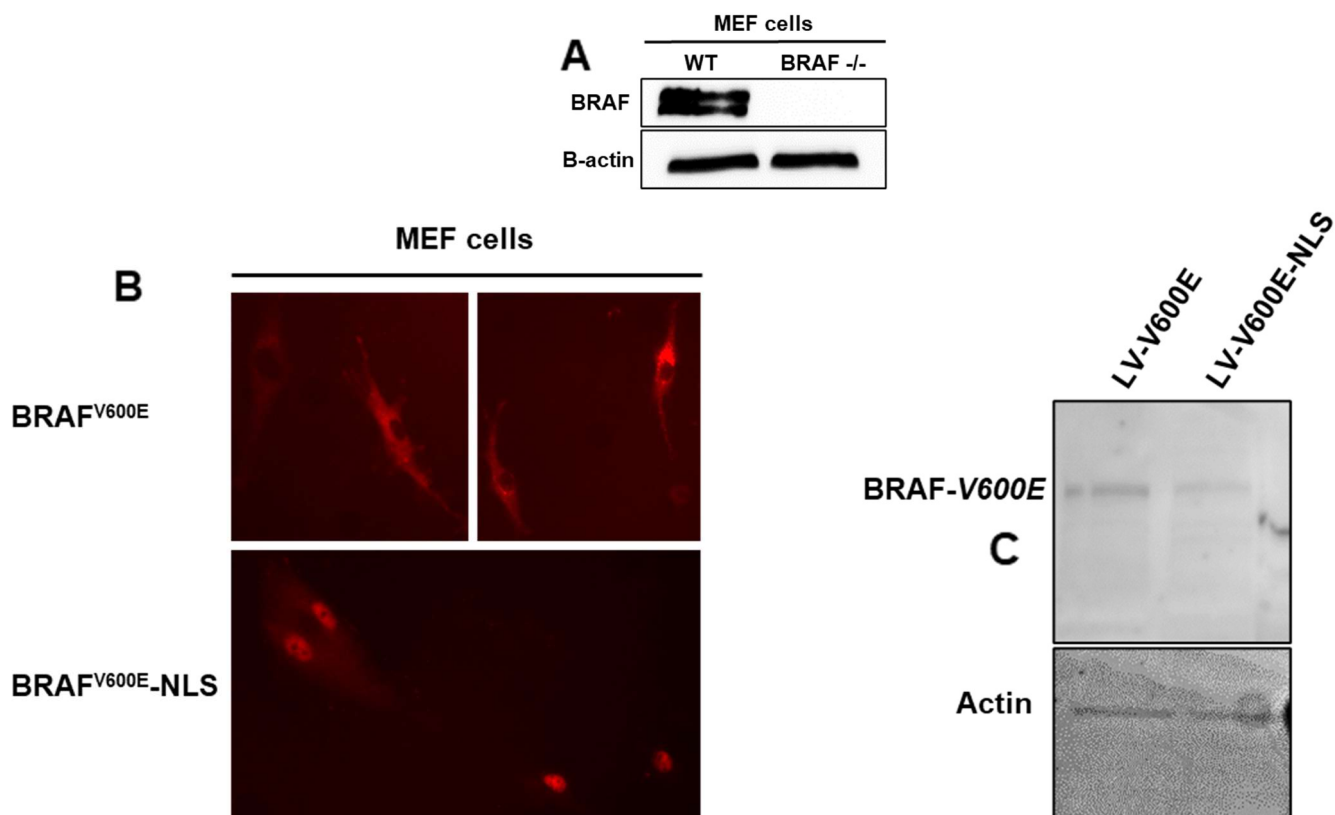
AFP	ErbB4	MMP-2
Amphiregulin	FGF basic	MMP-3
Angiopoietin-1	FoxC2	MMP-9
ANGPTL4	FKHR	MSP/MST1
ENPP-2/Autotaxin	Galectin-3	MUC-1
AXL	GM-CSF	Nectin-4
BCL-X	HCG	Osteopontin
CA125/MUC-16	HGF R/c-Met	p27/Kip1
E-Cadherin	HIF-1alpha	p53
VE-Cadherin	HNF-3beta	PDGF-AA
CAP-G	HO-1/HMOX1	CD31/PECAM-1
CA-9	ICAM-1/CD54	Progesterone R
Cathepsin B	CD25/IL-2 R alpha	Progranulin
Cathepsin D	IL-6	Prolactin
Cathepsin S	CXCL8/IL-8	Prostasin
CEACAM-5	IL-18 Bpa	E-Selectin
Decorin	KLK-3/PSA	Maspin
DKK-1	KLK-5	PAI-1/Serpin E1
DLL-1	KLK-6	SNAIL
EGF R/ErbB1	Leptin (OB)	SPARC
Endoglin/CD105	Lumican	Survivin
Endostatin	CCL2/MCP-1	Tenascin-C
Enolase 2	CCL8/MCP-2	THBS-1
eNOS	CCL7/MCP-3	TIE-2
EpCAM	M-CSF	UPA-1
ER-alpha	Mesothelin	VCAM-1
ErbB2	CCL3/MIP-1alpha	VEGF
ErbB3	CCL20/MIP-3alpha	Vimentin

**Figure S4.** The full list of the 84 cancer related proteins array.

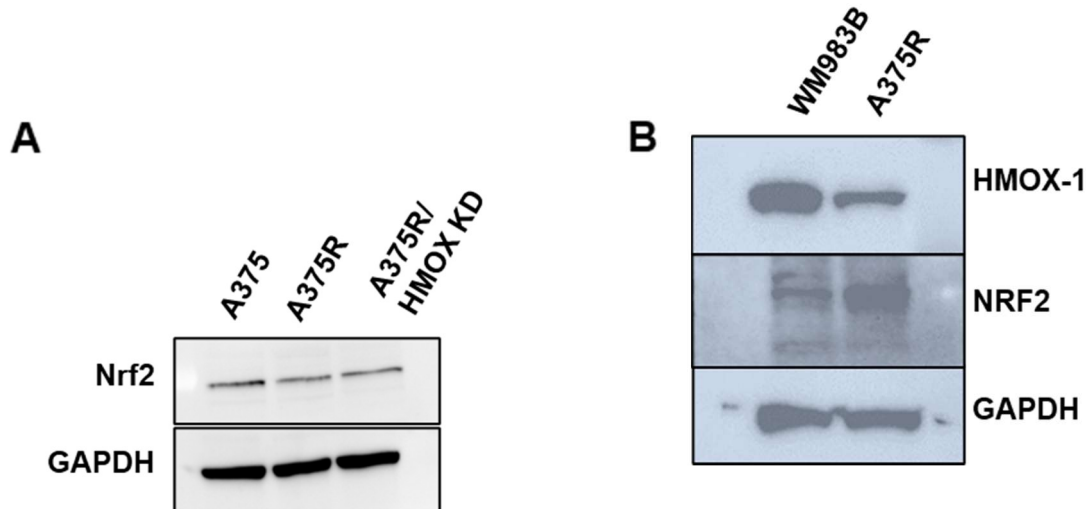
[https://www.rndsystems.com/products/proteome-profiler-human-xl-oncology-array\\_ary026](https://www.rndsystems.com/products/proteome-profiler-human-xl-oncology-array_ary026)



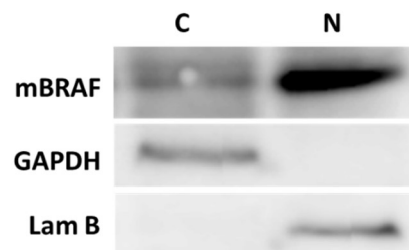
**Figure S5.** Suppression of HMOX-1 has an Anti-Proliferative Effect in WM983B Melanoma Cells. **(A)** HMOX1 expression in two resistant cell lines, A375R and WM983B. **(B)** HMOX1 knock down in WM983B cell line. **(C)** Invasion and colony formation assays before and after HMOX1 knock down in WM983B cells



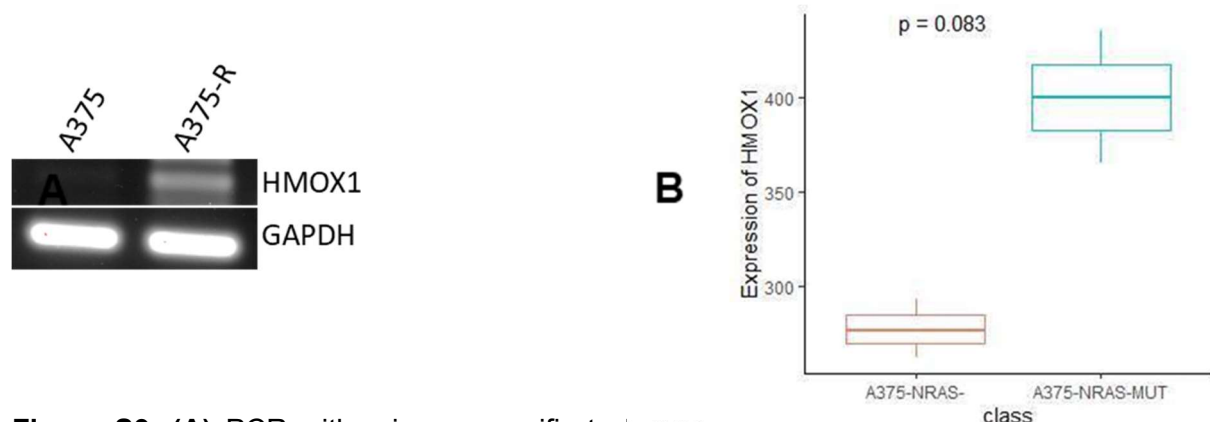
**Figure S6.** BRAF V600E and BRAF V600E -NLS expression in MEF  $-/-$  BRAF cells. **(A)** BRAF expression in WT and BRAF $-/-$  MEF. **(B)** LV-BRAF<sup>V600E</sup> and LV-BRAF<sup>V600E</sup>-NLS expression in MEF BRAF $-/-$  assessed by Immunofluorescence **(C)** LV-BRAF<sup>V600E</sup> and LV-BRAF<sup>V600E</sup>-NLS expression in MEF BRAF $-/-$  assessed by WB.



**Figure S7.** NRF2 expression in A375, A375R, A375R/HMOX KD and WM983B cells. **(A)** NRF2 expression in A375, A375R and A375R/HMOX1KD. **(B)** NRF2 expression in A375R and WM983B



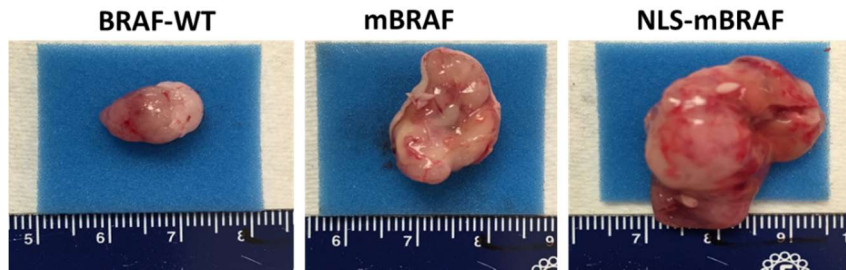
**Figure S8.** Cell fractionations from SkMel-28 cells (C: cytosolic; N: nuclear) were prepared and subjected to western blot analysis using anti-BRAFV600E (VE1 clone), Anti-GAPDH and anti-Lamin B antibodies



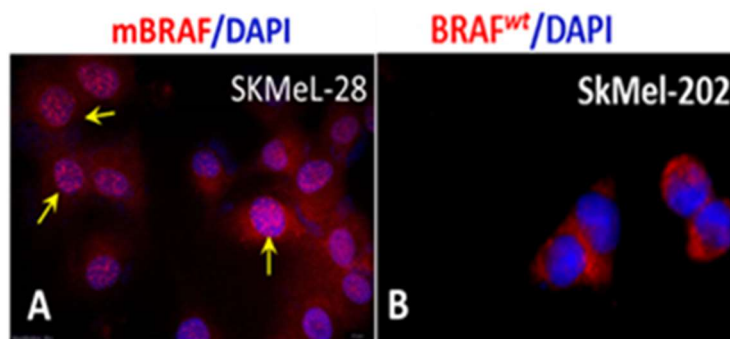
**Figure S9.** **(A)** PCR with primers specific to human. HMOX-1 or GAPDH. **(B)** *In vitro* model of A375 cell line treated with a BRAF inhibitor, HMOX1



was upregulated in the resistant clones, harboring a spontaneous NRAS mutation, compared to the sensitive clones ( $p=0.08$ ). GSE74729 GEO dataset (<https://www.ncbi.nlm.nih.gov/gds>).



**Figure S10.** Tumors from mice subcutaneously injected with MV3 cells with either nuclear localization signal (NLS)-BRAFFV600E or BRAFFV600E.



**Figure S11.** Nuclear localization of WT BRAF and BRAF V600E in melanoma cells. SkMel-28 and SkMel-202 Cells were grown in a complete RPMI medium, fixed with 4% formalin and stained with VE1 (SkMel-28) or Pan-BRAF (SkMel-202) antibodies and visualized by fluorescence Microscopy. Arrows indicate the nuclear localization of BRAF V600E; Mag: 400X.