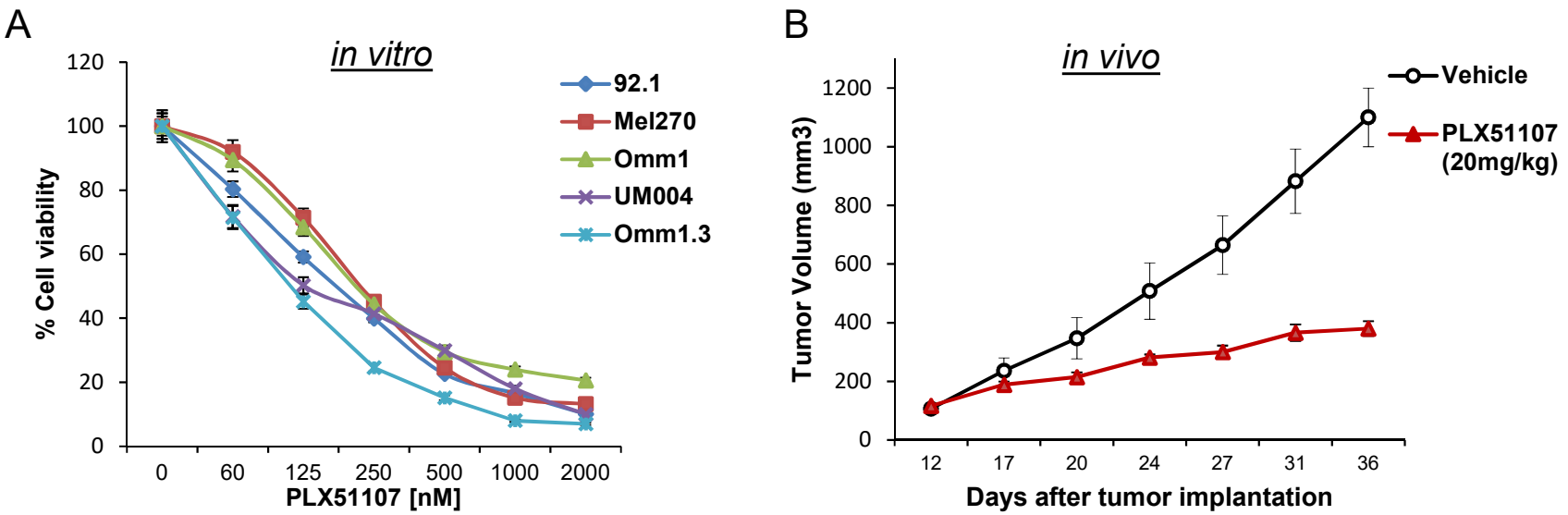
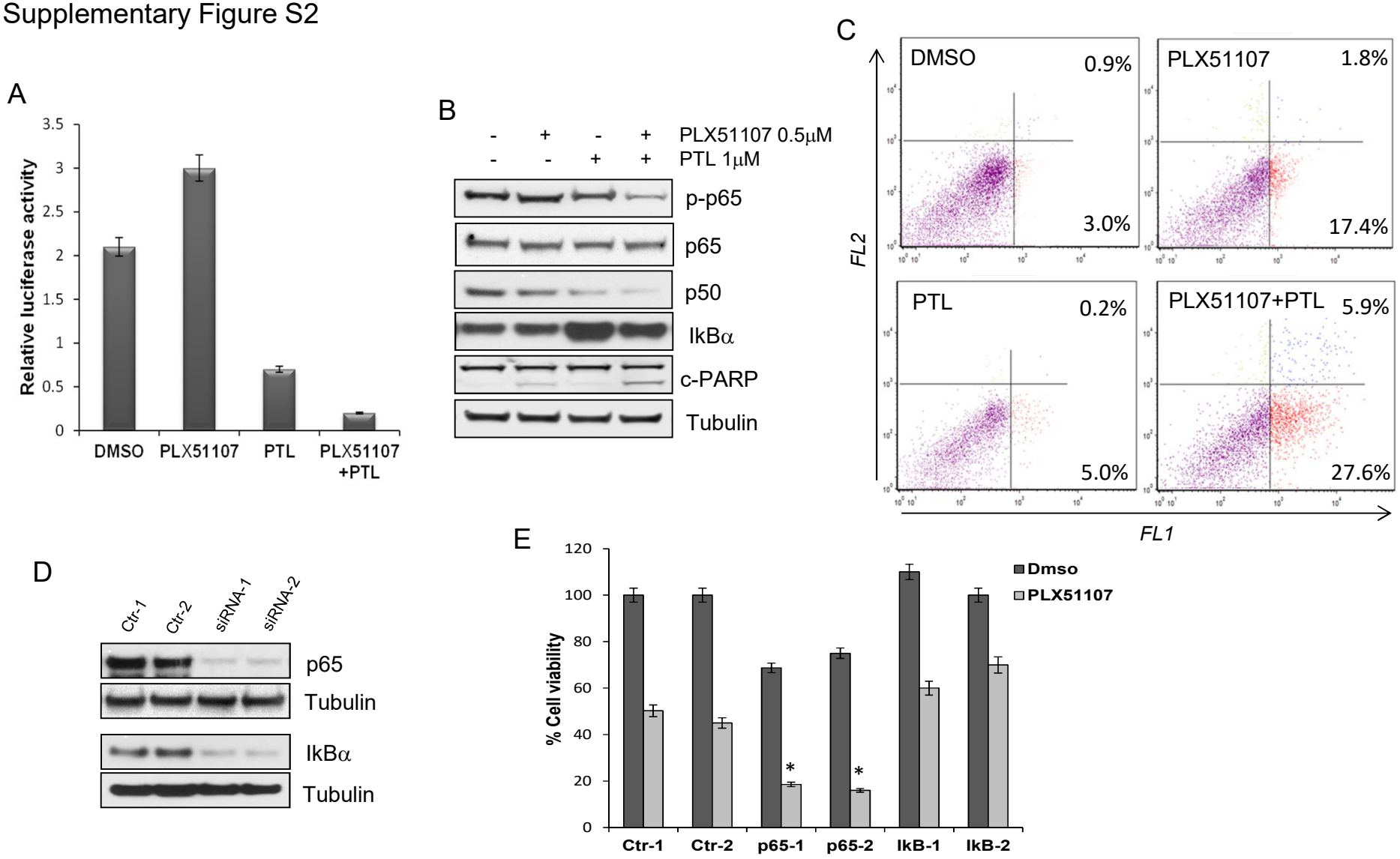
Supplementary Figure S1



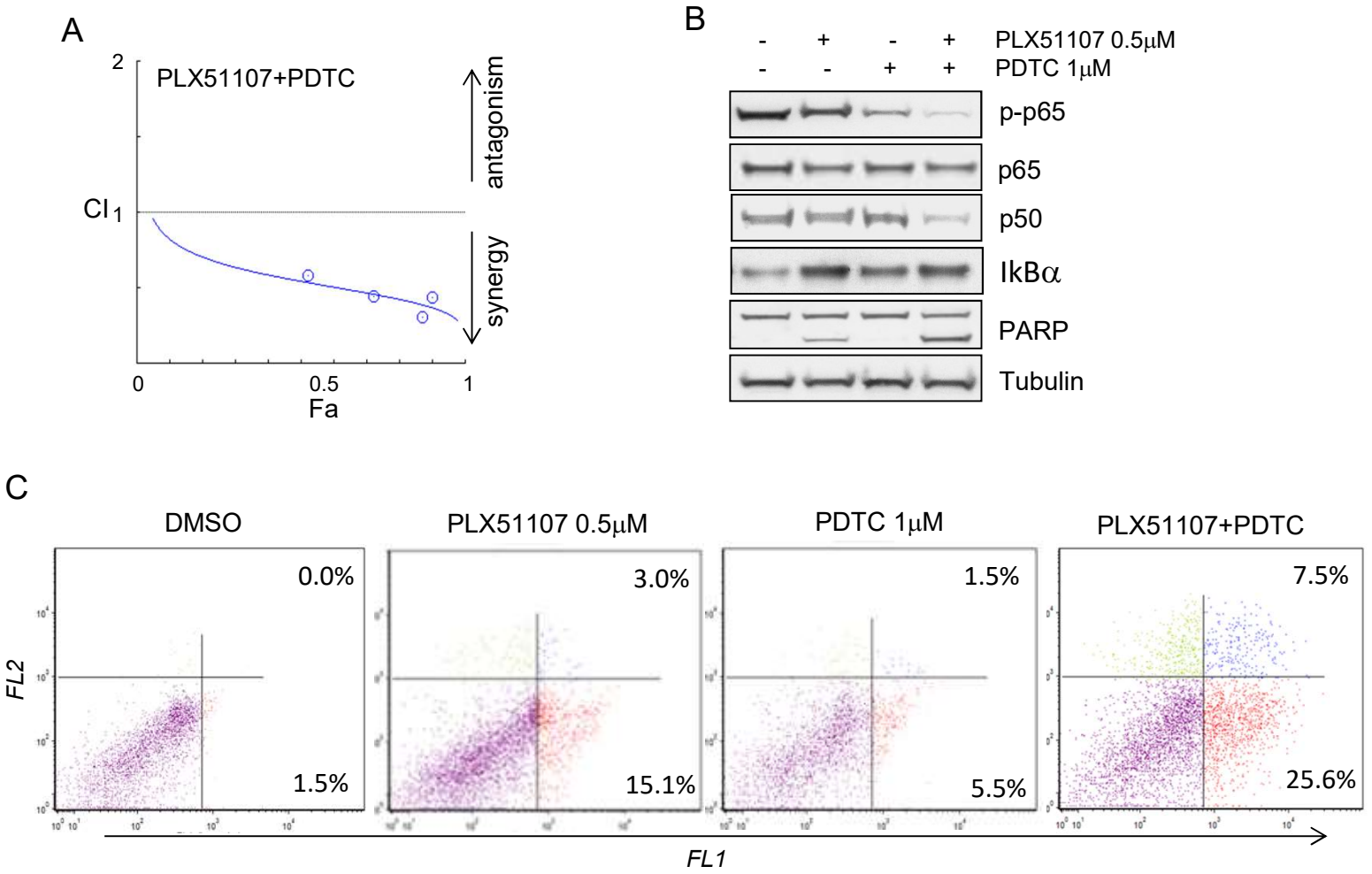
Supplementary Figure S1. PLX51107 inhibits the viability of UM cell lines *in vitro* and *in vivo*. A. UM cells were treated with increasing concentrations of PLX51107 (0.060-2.0μM) and analyzed for cell viability after 3 days. Data are representative of three independent experiments, mean ± sd. **B.** PLX51107 has antitumor effects in mouse xenografts. UM cells (92.1) were injected into the right flank of 8 week old nu/nu SCID male mice. When subcutaneous tumors were approximately 100 mm^3 diameter, the mice were treated with vehicle, PLX51107 (20mg/kg/d), 5 days/week for 3 weeks. Tumor volumes were measured with calipers every 2 to 3 days. Each value represents the mean measurement of 5 mice ±SEM.

Supplementary Figure S2



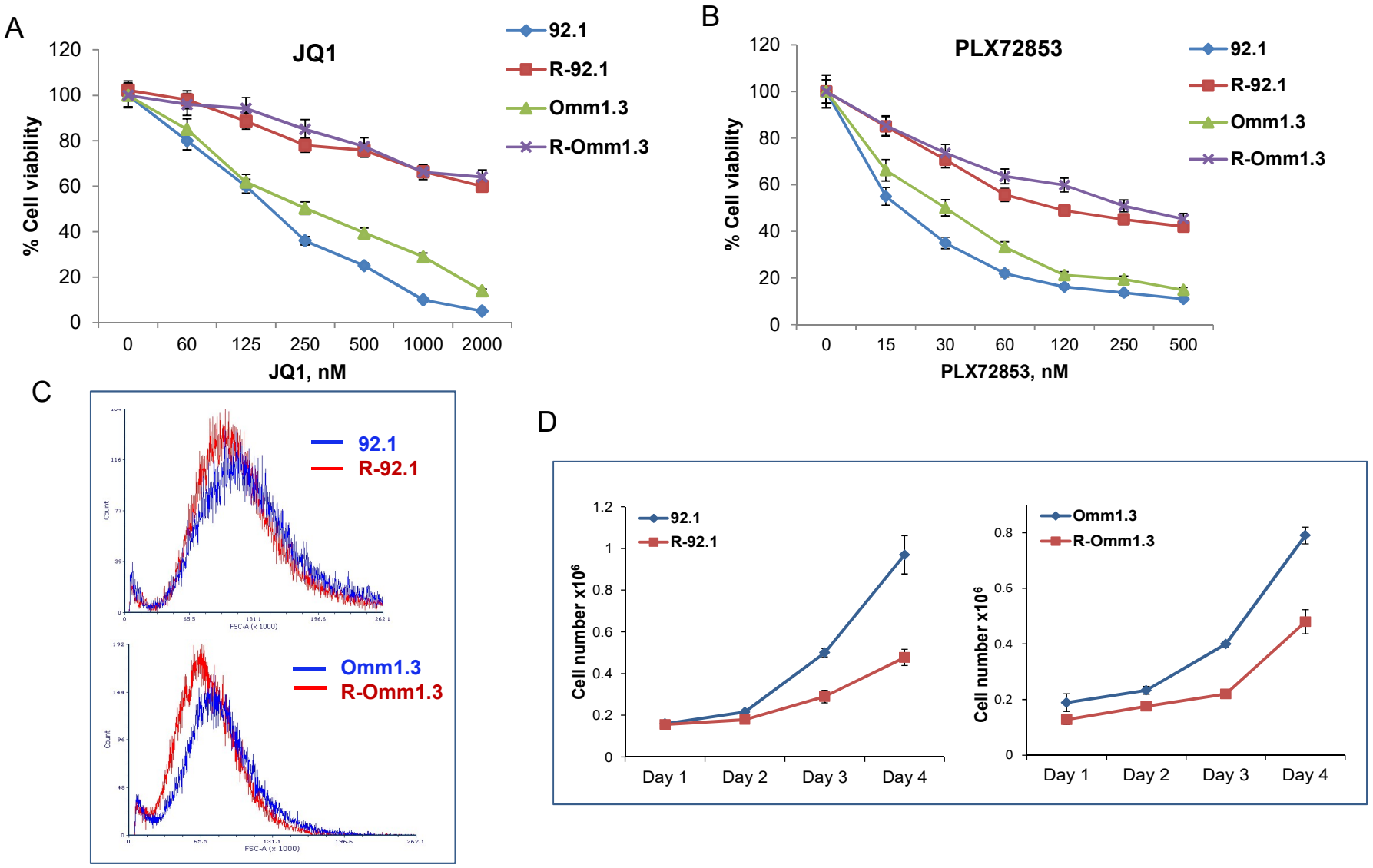
Supplementary Figure S2. PTL inhibits NF-kB activity and induces apoptosis in combination with PLX51107. A. NF-kB and renilla luciferase reporter gene vectors were transfected in Omm1.3 cells, then treated with 0.5μM PLX51107, 1μM PTL and the combination for 24hrs. Results are normalized to renilla luciferase activity and represent the mean ± sd. **B.** Western blot analysis of Omm1.3 cells treated with 0.5μM PLX51107, 1μM PTL and the combination. **C.** Apoptosis assay of Omm1.3 cells treated with 0.5μM PLX51107 and 1μM PTL as single agents and in combination for 48hrs. **D.** Western blot analysis of Omm1.3 cells showing depletion of p65 and IkBα after siRNA transfection. **E.** Cell viability assay of siRNA-transfected cells after treatment with 0.5μM PLX51107 for 72 hrs. Bars, mean ± sd *p<0.002

Supplementary Figure S3



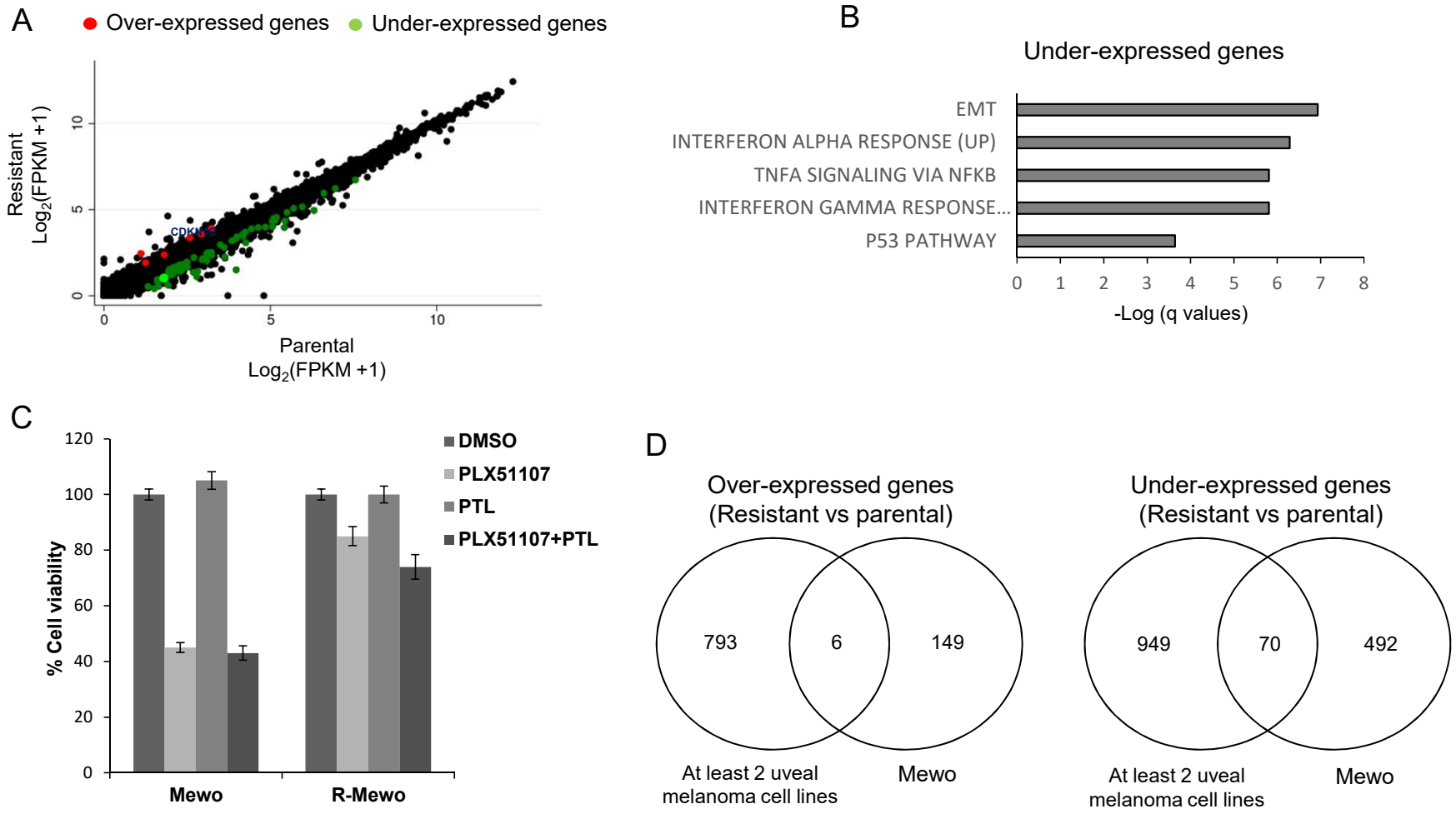
Supplementary Figure S3. The NF-kB inhibitor PDTC has synergistic activity with the BET inhibitor PLX51107. A. Synergy was calculated with the Chou-Talalay method. Combination indexes < 1. **B.** Western blot analysis of 92.1 cells treated with 0.5μM PLX51107 and 1μM PDTC as single agents and in combination for 48hrs, showing the inhibition of p65 phosphorylation and p50 expression, and the induction of IkBα and PARP cleavage. **C.** Apoptosis assay measuring cell permeability to fluorescent stains YO-PRO and propidium iodide.

Supplementary Figure S4



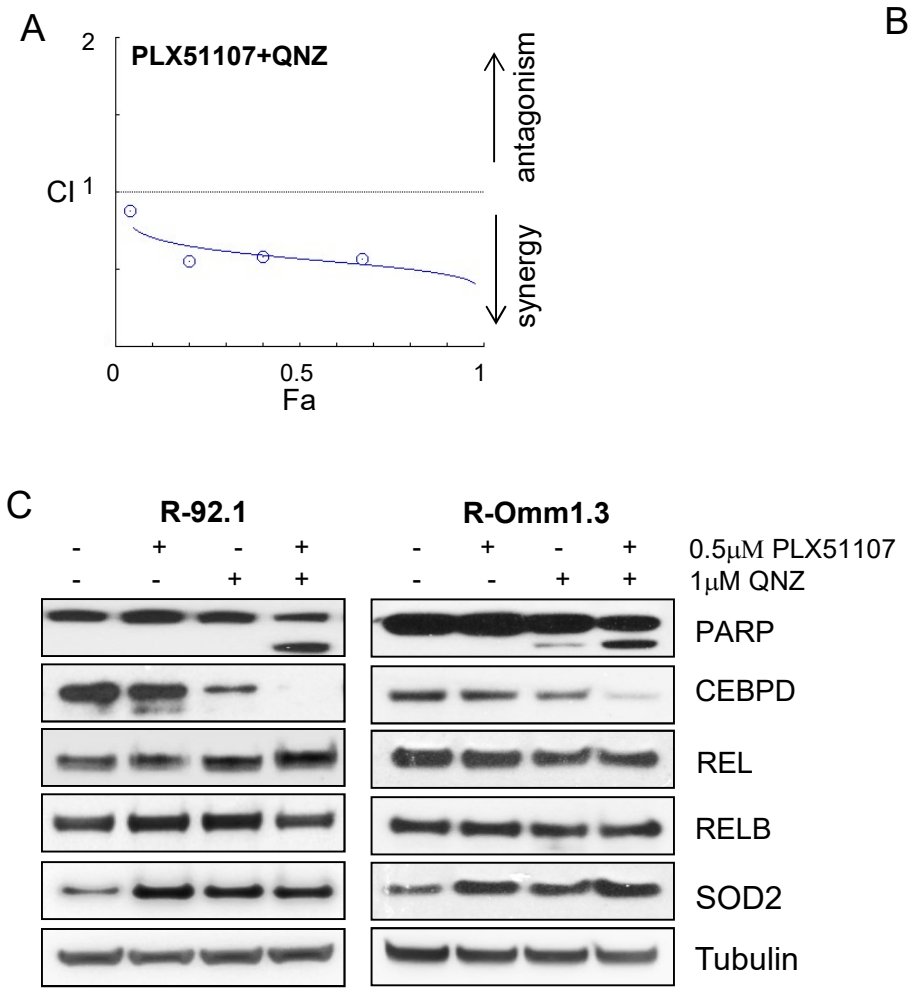
Supplementary Figure S4. UM cells resistant to PLX51107 show cross-resistance to other BET inhibitors. Parental and resistant cells were treated with increasing doses of the BRD4 inhibitor JQ1 (**A**) or the pan-BET inhibitor PLX72583 (**B**), and tested in cell viability assays after 72hrs. Each point is a mean ± sd. **C.** Parental and BETi-resistant 92.1 and Omm1.3 cells were analyzed for cell size by flow cytometry. **D.** The resistant cells showed slower rates of growth compared to the parental cells. Cell number was measured each day for four days. Each point is a mean ± sd.

Supplementary Figure S5



Supplementary Figure S5. BETi-resistant cutaneous melanoma and UM cells have different gene expression profiles. A. Scatter plot showing highlighted in red and green genes that are over or under expressed in Mewo and at least two UM cell lines. **B.** GSEA for differentially under-expressed genes in the Mewo resistant cells. There was no enriched pathway for overexpressed genes. **C.** Parental and resistant Mewo cells were treated with 0.5μM PLX51107 and 1μM PTL and cell viability was tested after 72h . Bars are means ± sd. **D.** The overlap between cutaneous and uveal DE gene-set is small as shown in the Venn-diagram.

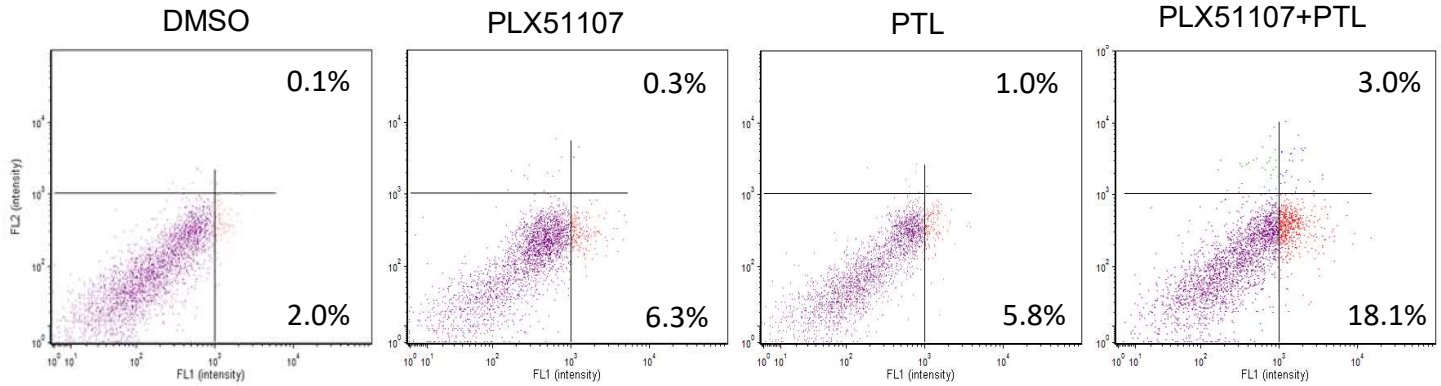
Supplementary Figure S6



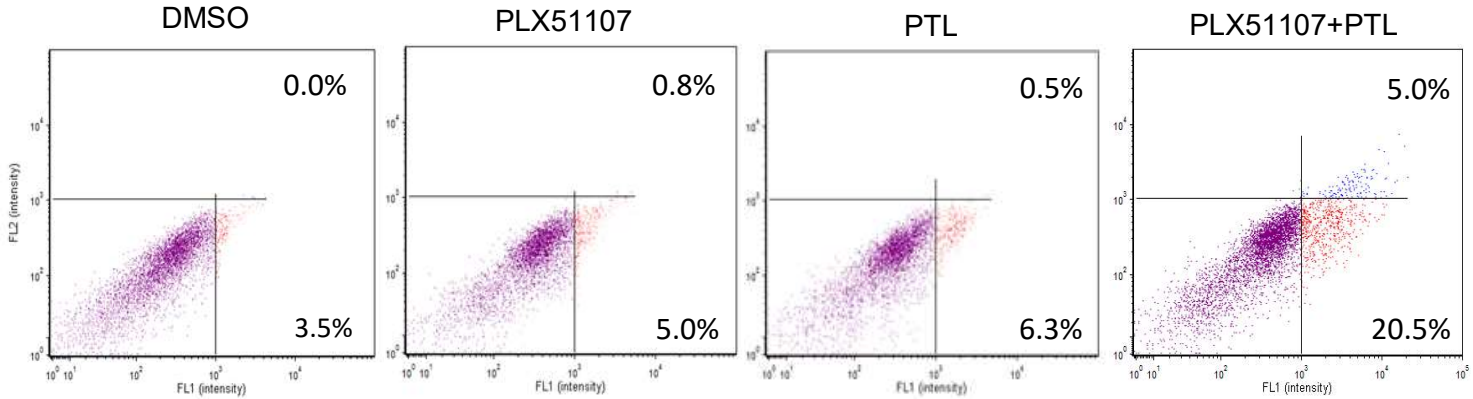
Supplementary Figure S6. Synergistic effects of the NF-kB inhibitor QNZ in combination with PLX51107 in the BETi-resistant UM cells. A. The resistant cells R-92.1 were treated with increasing doses of PLX51107 and QNZ for 72h. Synergy was calculated with the Chou-Talalay method, (CI<1). **B.** Apoptosis assay of R-92.1 cells treated with 0.5μM PLX51107, 1μM PTL alone and in combination for 48h, measuring cell membrane permeability to fluorescent stains YO-PRO and propidium iodide. **C.** R-92.1 and R-Omm1.3 cells were analyzed by immunoblotting after treatment with 0.5μM PLX51107, 1μM QNZ and the combination for 48h. The combination treatment suppressed the expression of CEBPD and induced PARP cleavage. The expression of REL, RELB, SOD2 and tubulin are also shown.

Supplementary Figure S7

A **R-92.1**

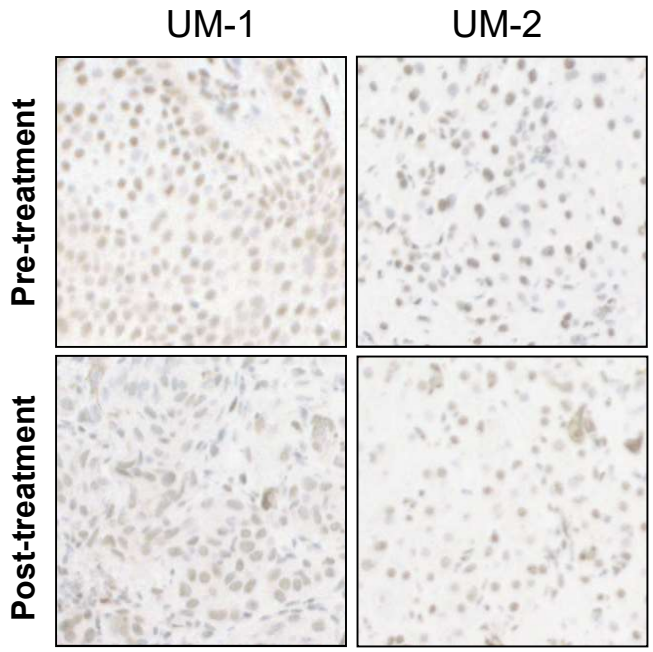


B **R-Omm1.3**



Supplementary Figure S7. The combination PLX51107+PTL induces apoptosis in the BETi-resistant cells. Apoptosis assays of R-92.1 (**A**) and R-Omm1.3 (**B**) cells treated with 0.5μM PLX51107, 1μM PTL and the combination for 48h, measuring cell membrane permeability to fluorescent stains YO-PRO (FL1) and propidium iodide (FL2).

Supplementary Figure S8



Supplementary Figure S8. Immunohistochemical analysis of p-p65 expression before and after 2 weeks of treatment with PLX51107 in liver biopsies of two representative patients with UM. No significant changes in p-p65 staining were observed after treatment.

Supplementary Table S1

Gene	Company/Assay ID	siRNA (Sense)
RELA (p65)-1	Dharmacon J-003533-06-0002	GGAUUGAGGAGAAACGUAA
RELA (p65)-2	Santa Cruz Biotech/ sc-29410	GCCCUAUCCCUUUACGUC
IκBα-1	Dharmacon J-003533-06-0002	GGAGGCCAGCGUCUGACGU
IκBα-2	Thermo Fisher/121868	GAGUCAGAGUUCACGGAGU
CEBPD-1	Santa Cruz Biotech/ sc-37722	GACAUAGGAGCGCAAAGAA CCACUAAACUGCGAGAGAA GAGAGAAGCUAAACGUGUU
CEBPD-2	Thermo Fisher/15987	GGAAAAGACUGAGCAUGCU
REL-1	Santa Cruz Biotech/ sc-29857	CAAGACUUCUGAGCAUGAA GCAAUUGAGUGACUCCUUU GUGACUCCUUUCCAUAUGA
REL-2	Thermo Fisher/106896	GGCAUCUUUUCACAAGCUG
RELB-1	Santa Cruz Biotech/ sc-36402	GCAACAUGUUCCCCAAUCA CGUGCACUAGCUUGUUACA CUCCAGUAGGAUUCGGAAA
RELB-2	Thermo Fisher/115798	GCACAGAUGAAUUGGAGAU
SOD2-1	Santa Cruz Biotech/ sc-41655	CGAUCGUUAUGCUGAUCAU GCAUCAAGCCUGGUACAUA CCUAUAAGGUCCUGGAUAA
SOD2-2	Thermo Fisher/260737	GCAUCUGUUGGUGUCCAAG
Control-1	Santa Cruz Biotech/ sc-37007	UUCUCCGAACGUGUCACGU
Control-2	Dharmacon D-001810-10-20	UGGUUUACAUGUCGACUAA UGGUUUACAUGUUGUGUGA UGGUUUACAUGUUUUCUGA UGGUUUACAUGUUUUCCUA