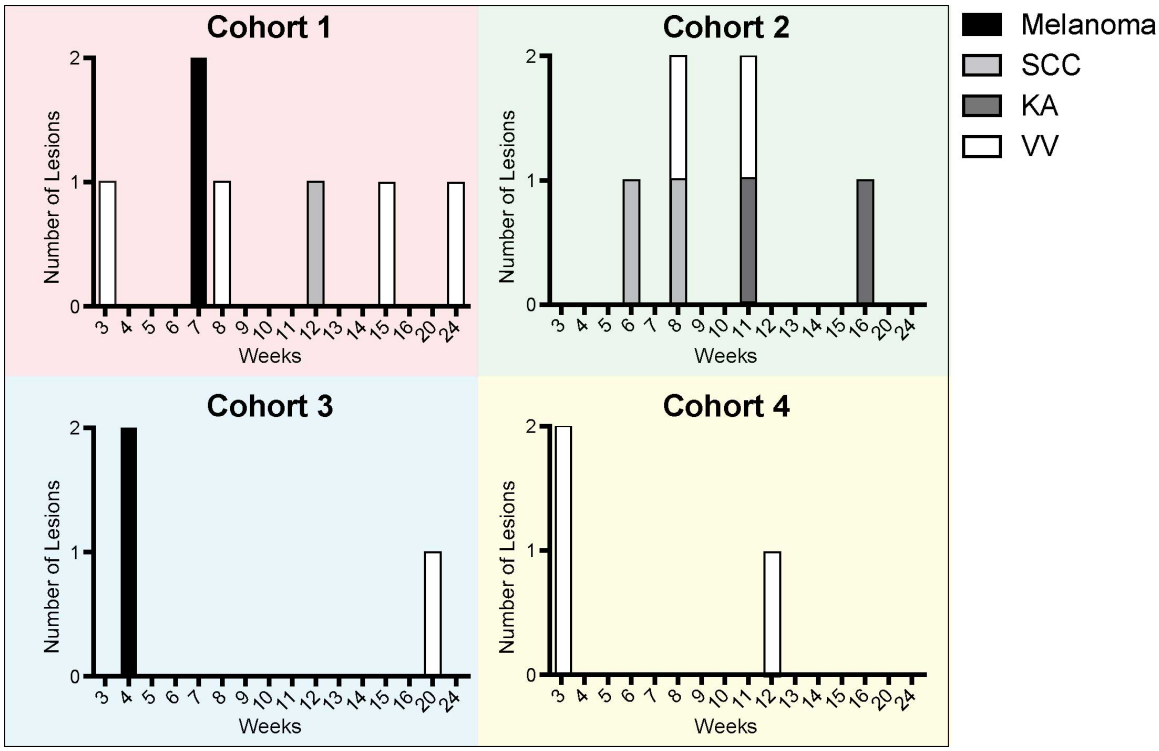
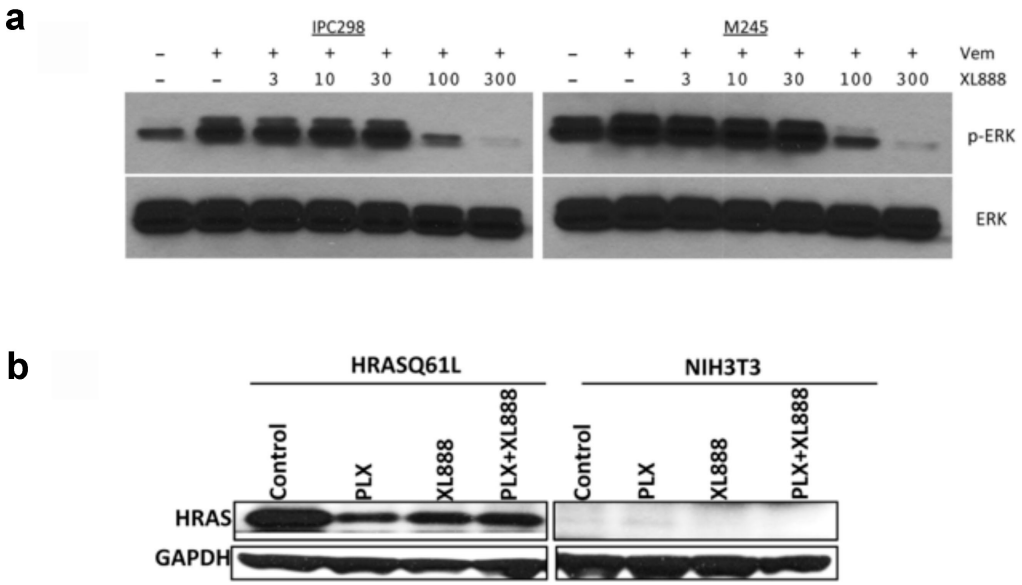


Supplemental Figure 1: Incidence of secondary proliferative lesions per cohort, sorted by number of lesions and week on therapy. Data shows the numbers of secondary melanoma, SCC, KA and VV per cohort over time.

Cohort	Patient	Lesions	Time of Diagnosis
1	1	1 VV	Week 8
1	2	1 VV 2 melanoma 1 SCC	Week 3 Week 7 Week 12
1	3	2 VV	Week 15 and 24
2	1	1 SCC 1 VV 1 KA	Week 8 Week 11 Week 11
2	2	-	-
2	3	1 SCC 1 VV 1 KA	Week 6 Week 8 Week 16
3	1	2 melanoma	Week 4
3	2	1 VV	Week 20
3	3	-	-
4	1	-	-
4	2	-	-
4	3	-	-
4	4	-	-
4	5	2 VV	Week 3
4	6	1 VV	Week 12

Supplemental Table 1: Data on the incidence of proliferative skin lesions per dose cohort for each individual patient. Data includes type of lesion and time of diagnosis.



Supplemental Figure 2: a: Concentrations of XL888 >100nM are required to inhibit the paradoxical activation of ERK. *NRAS*-mutant melanoma cell lines (IPC-298 and M245) were treated with vemurafenib (1 uM) in the absence and presence of increasing concentration of XL888 for 72 hrs. Western blot shows phospho-ERK and total ERK. **b:** Expression levels of HRAS in NIH3T3 cells transfected with a plasmid for HRAS Q61L.