Supplementary Figure legends

Fig. S1. Survival Curves for VEM resistant lines. A set of melanoma cell lines (A375, SK-Mel-28, UACC903, MGH-MC-1, K4, WM239 and WM1158) were induced into VEM resistance by sequentially exposing these cells to escalating doses of VEM. Cell viability assays for each sensitive/resistant pair were performed by treating cells with VEM for 72 hr. Error bars indicate mean viability ± SEM (n=3).

Fig. S2. EphA2 inhibitor–kinase interaction maps. Small molecule–kinase interaction maps for ALWII-41-27 (A) and HG-6-64-1 (B). Kinases found to bind are marked with red circles, where larger circles indicate higher-affinity binding. Interactions with percentage control <1% are shown.

Fig. S3. Validation of EphA2 as the target of EphA2 inhibitors. (A-C) EphA2 inhibitors exhibited a stronger inhibition of viability in cells with higher EphA2 levels (CHL-1) compared to those with lower EphA2 levels (SK-Mel-119). (D-I) Expression of EphA2 in SK-mel-119 and WM164 cells sensitized these cells to both ALW-II-41-27 and HG-6-64-1 thereby suggesting that the compounds exerted their inhibitory activity through EphA2. (J-O) In contrast, when melanoma cells were depleted of EphA2, both ALW-II-41-27 and HG-6-64-1 were less effective. (P-R) A weaker EphA2 inhibitor (NG-25) exhibited less cellular inhibition compared to the more active compound ALW-II-41-27 in A375 (P), MGH-MC-1 (Q) and K4 (R) lines. Error bars indicate mean viability ± SEM (n=3).

Fig. S4. EphA2 inhibitors suppressed the viability of VEM sensitive and resistant BRAF mutant cell lines and NRAS mutant cell lines. (A,B) EphA2 inhibitors reduced the viability of both matched VEM sensitive and resistant cells. Error bars indicate mean viability ± SEM (n=3). (C) EphA2 inhibitors induced cell death in VEM insensitive (CHL-1), sensitive (A375) and matched resistant (A375-P) cells. Representative bright field images of cells are shown.

Fig. S5. ALW-II-41-27 suppresses *in vivo* tumor growth of both VEM sensitive and resistant melanomas. Administration of ALW-II-41-27 inhibits growth of both A375 (A) and A375-P (B) tumors in vivo. After inoculation of 4×10^7 A375 and A375-P cells, ALW-II-41-27 was administered twice a day by intraperitoneal injection (30 mg/kg) while PLX-4720 was administered once a day by intraperitoneal injection (30 mg/kg). After treatment, the mice were euthanized using CO_2 and photographed. Then the tumors were harvested and photographed. (C) ALW-II-41-27 significantly inhibited the growth of tumors in both A375 and A375P cells while VEM only inhibited growth of A375 tumors. Error bars indicate mean tumor volume ± SEM (n=6 each arm). (D,E) Neither ALW-II-41-27 nor VEM dramatically reduced the body weight of mice during the treatments. $^{**}P<0.001$ by Students' *t* test.