Supplementary figures

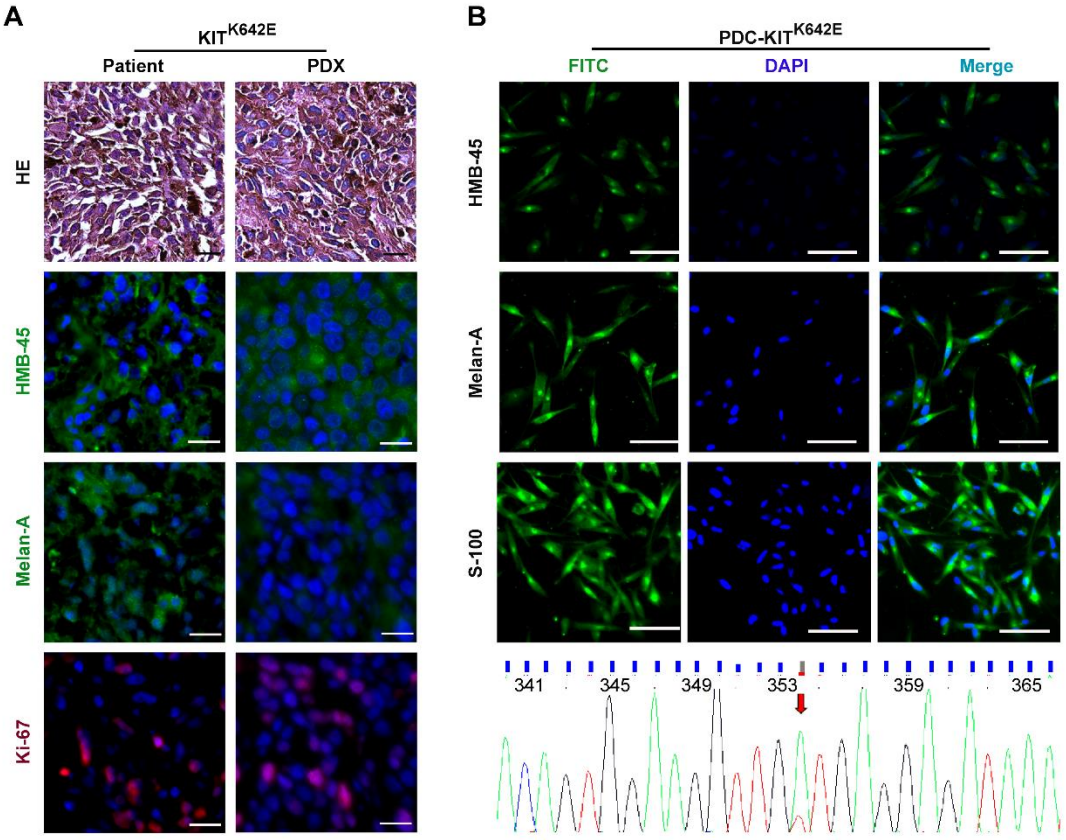


Figure S1. Establishment and characterization of *KIT*^{K642E} PDX models. **(A)** Representative hematoxylin and eosin (H&E) staining and immunofluorescence staining of patient tumors and corresponding PDXs. HMB-45 and Melan-A (both green), Ki67 (red) and DAPI (blue). The scale bar is 100 μm. **(B)** Representative immunofluorescence staining of PDX-derived cells is shown in the upper panel, and the *KIT* mutation status of the corresponding PDX-derived cells is shown in the bottom panel.HMB-45, Melan-A and S-100 (both green) and DAPI (blue). The scale bar is 100 μm.

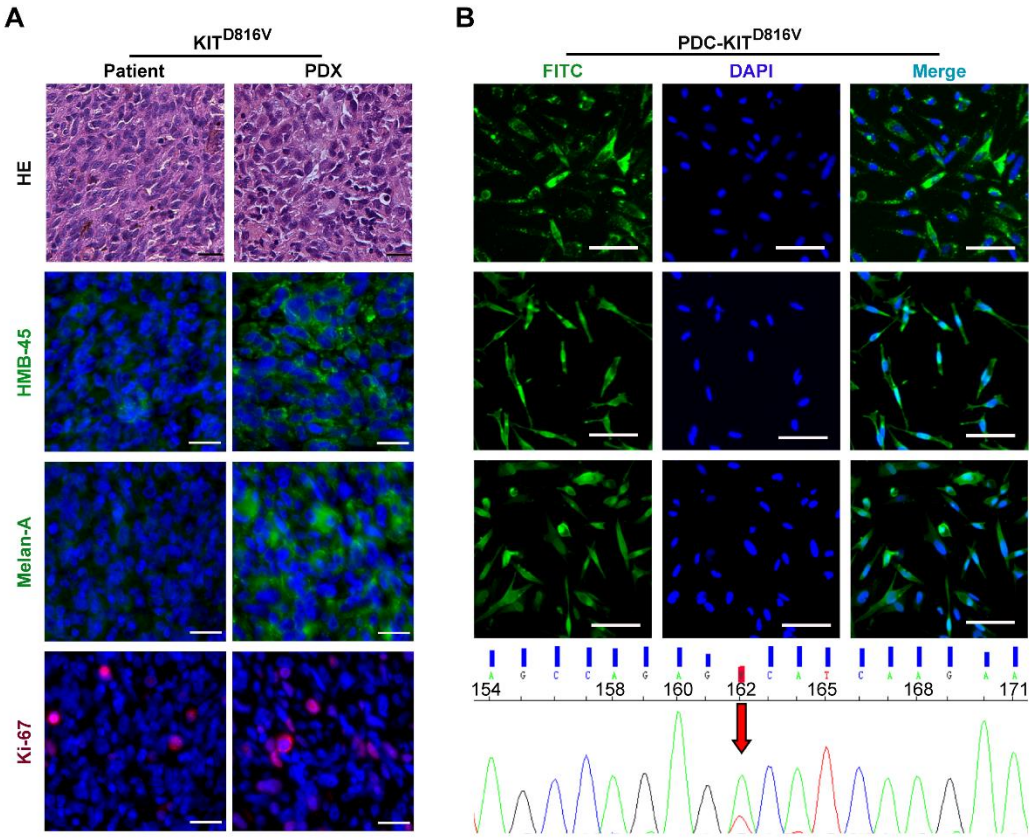


Figure S2. Establishment and characterization of *KIT*^{D816V} PDX models. **(A)** Representative hematoxylin and eosin (H&E) staining and immunofluorescence staining of patient tumors and corresponding PDXs. HMB-45 and Melan-A (both green), Ki67 (red) and DAPI (blue). The scale bar is 100 μm. **(B)** Representative immunofluorescence staining of PDX-derived cells is shown in the upper panel, and the *KIT* mutation status of the corresponding PDX-derived cells is shown in the bottom panel.HMB-45, Melan-A and S-100 (both green) and DAPI (blue). The scale bar is 100 μm.

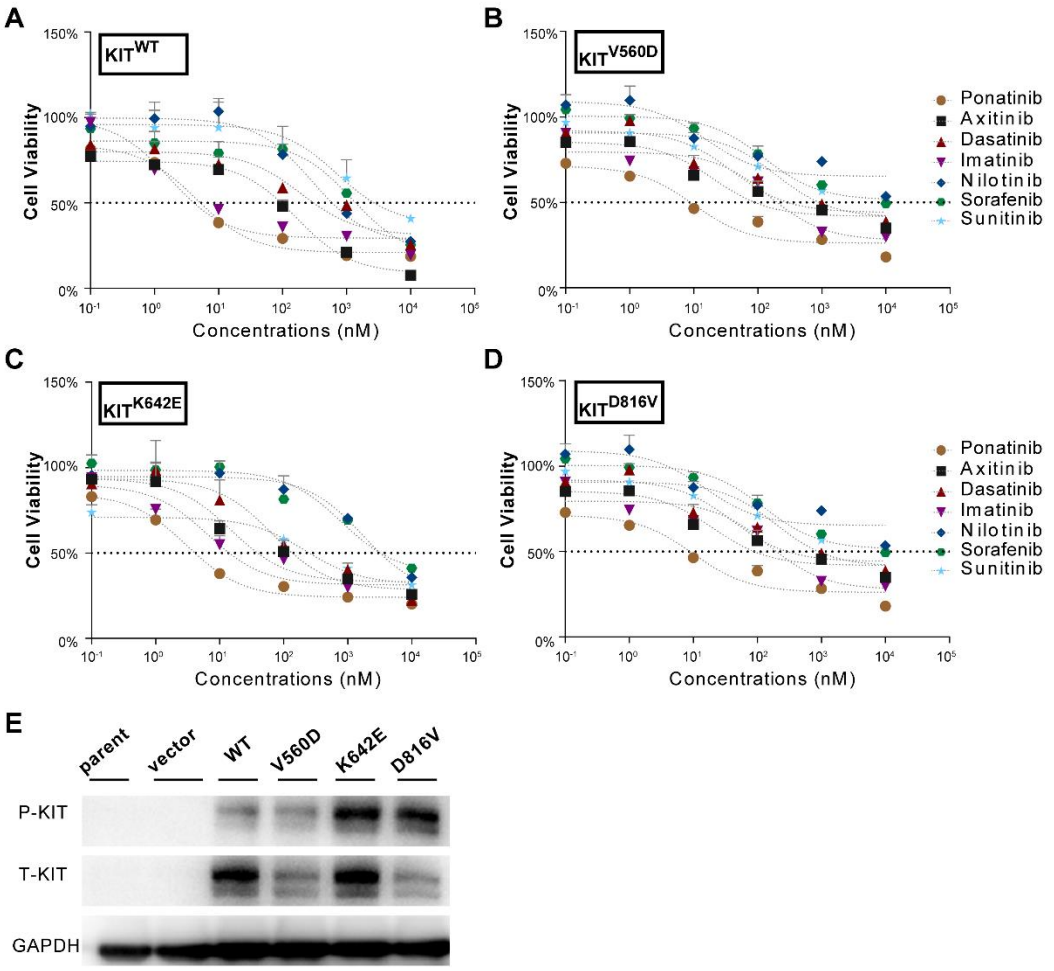


Figure S3. Dose-response curve of imatinib, dasatinib axitinib, nilotinib, ponatinib, sorafenib, and sunitinib in 72-h proliferation assays in Ba/f3 cell lines transfected with *KIT*^{WT}, *KIT*^{V560D}, *KIT*^{K642E} and *KIT*^{D816V}. **(A)** Inhibitory efficacy of inhibitors in Ba/f3 cell lines transfected with *KIT*^{WT}. **(B)** Inhibitory efficacy of inhibitors in Ba/f3 cell lines transfected with *KIT*^{V560D}. **(C)** Inhibitory efficacy of inhibitors in Ba/f3 cell lines transfected with *KIT*^{K642E}. **(D)** Inhibitory efficacy of inhibitors in Ba/f3 cell lines transfected with and *KIT*^{D816V}. **(E)** Expression of *KIT* in transfected Ba/F3 cells.

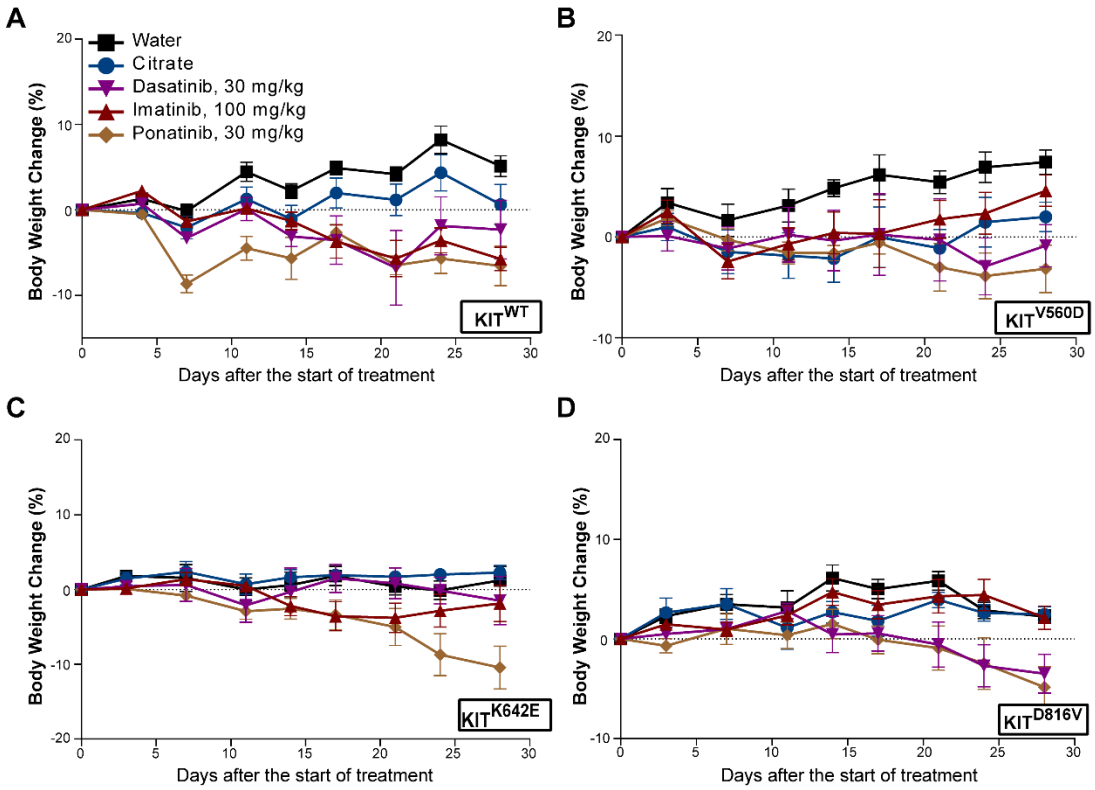


Figure S4. Treatment toxicity evaluation in PDXs. Treatment relative toxicities were determined by body weight during the treatment. **(A)** PDX with *KIT*^{WT}. **(B)** PDX with *KIT*^{V560D} mutation. **(C)** PDX with *KIT*^{K642E} mutation. **(D)** PDX with *KIT*^{D816V} mutation.

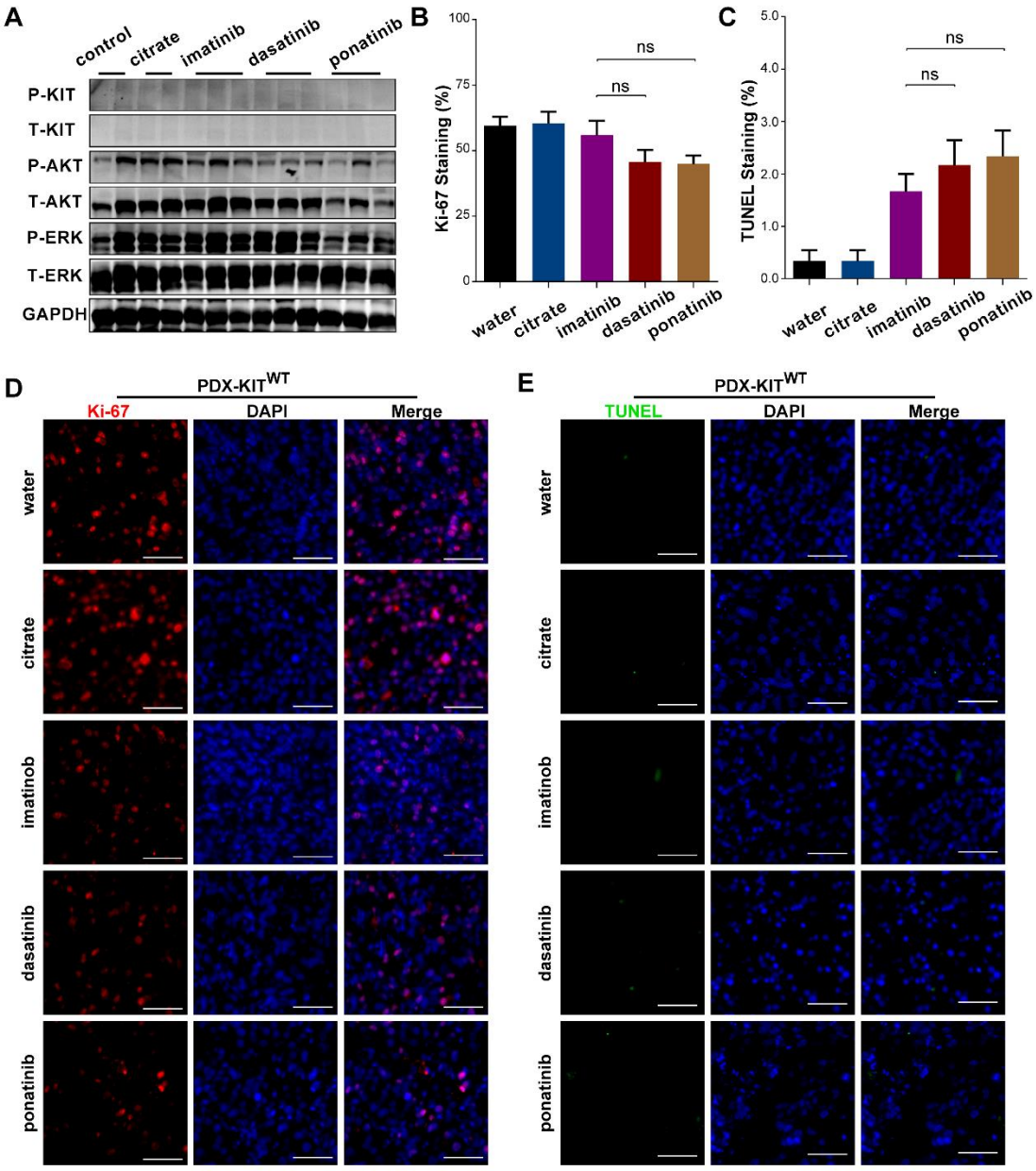


Figure S5. Inhibitory efficacy of ponatinib in PDX-*KIT*^{WT}. **(A)** Immunoblot analysis of *KIT* signaling in tumors after 28 days of treatment with imatinib, dasatinib and ponatinib. **(B)** Scoring of Ki-67 staining is summarized as the mean ± SEM. Student's *t*-test, $P > 0.05$; ns, not significant. **(C)** Scoring of TUNEL staining is summarized as the mean ± SEM. Student's *t*-test, $P > 0.05$; ns, not significant. **(D)** Representative Ki-67 staining in tumors after 28 days of treatment with imatinib, dasatinib and ponatinib. Scale bar, 50μm. **(E)** Representative TUNEL staining in tumors after 28 days of treatment with imatinib, dasatinib and ponatinib. Scale bar, 50μm.

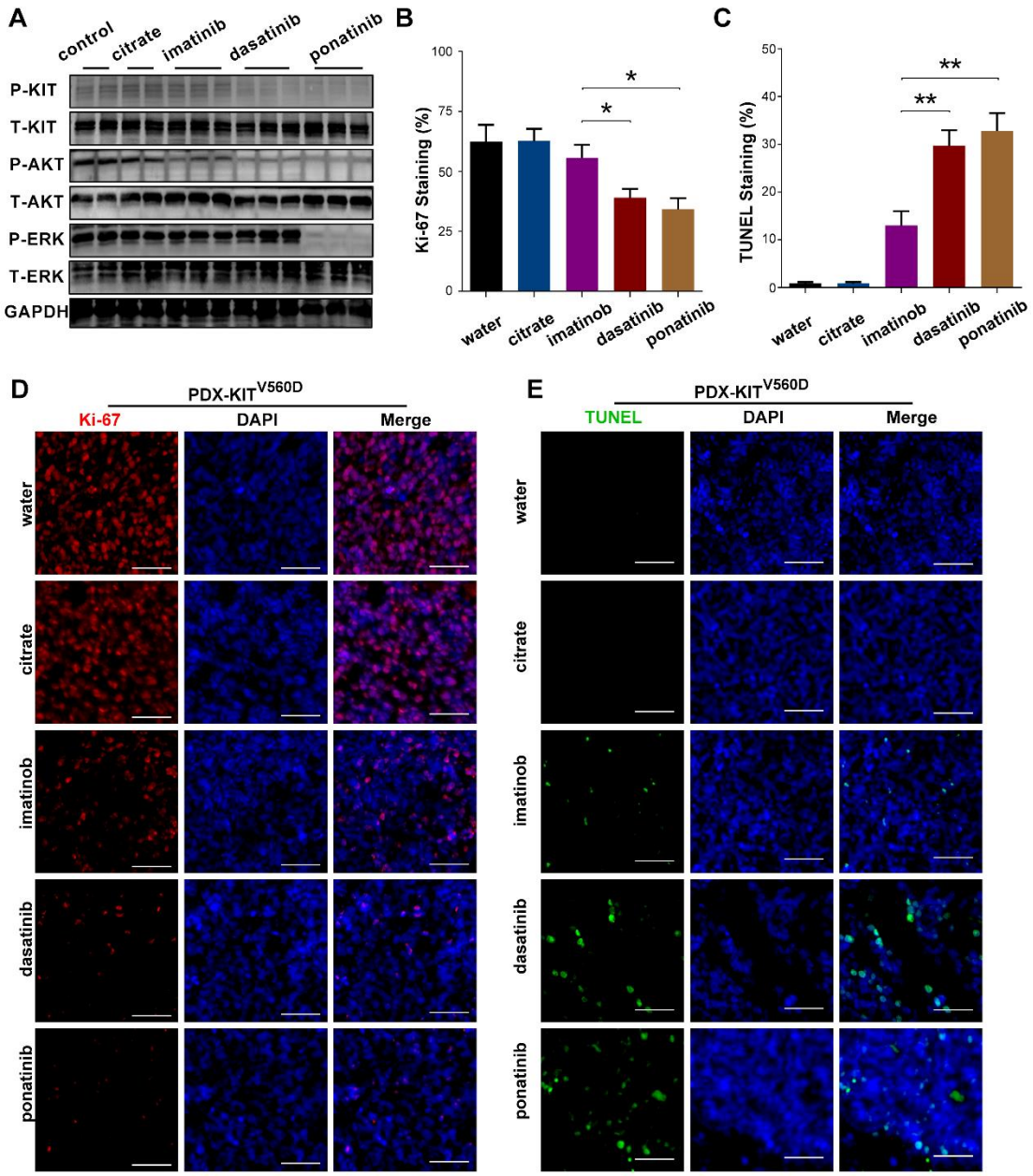


Figure S6. Inhibitory efficacy of ponatinib in PDX with *KIT*^{V560D} mutation. **(A)** Immunoblot analysis of *KIT* signaling in tumors after 28 days of treatment with imatinib, dasatinib and ponatinib. **(B)** Scoring of Ki-67 staining is summarized as the mean ± SEM. Student's *t*-test, *, $P < 0.05$. **(C)** Scoring of TUNEL staining is summarized as the mean ± SEM. Student's *t*-test, **, $P < 0.01$. **(D)** Representative Ki-67 staining in tumors after 28 days of treatment with imatinib, dasatinib and ponatinib. Scale bar, 50μm. **(E)** Representative TUNEL staining in tumors after 28 days of treatment with imatinib, dasatinib and ponatinib. Scale bar, 50μm.

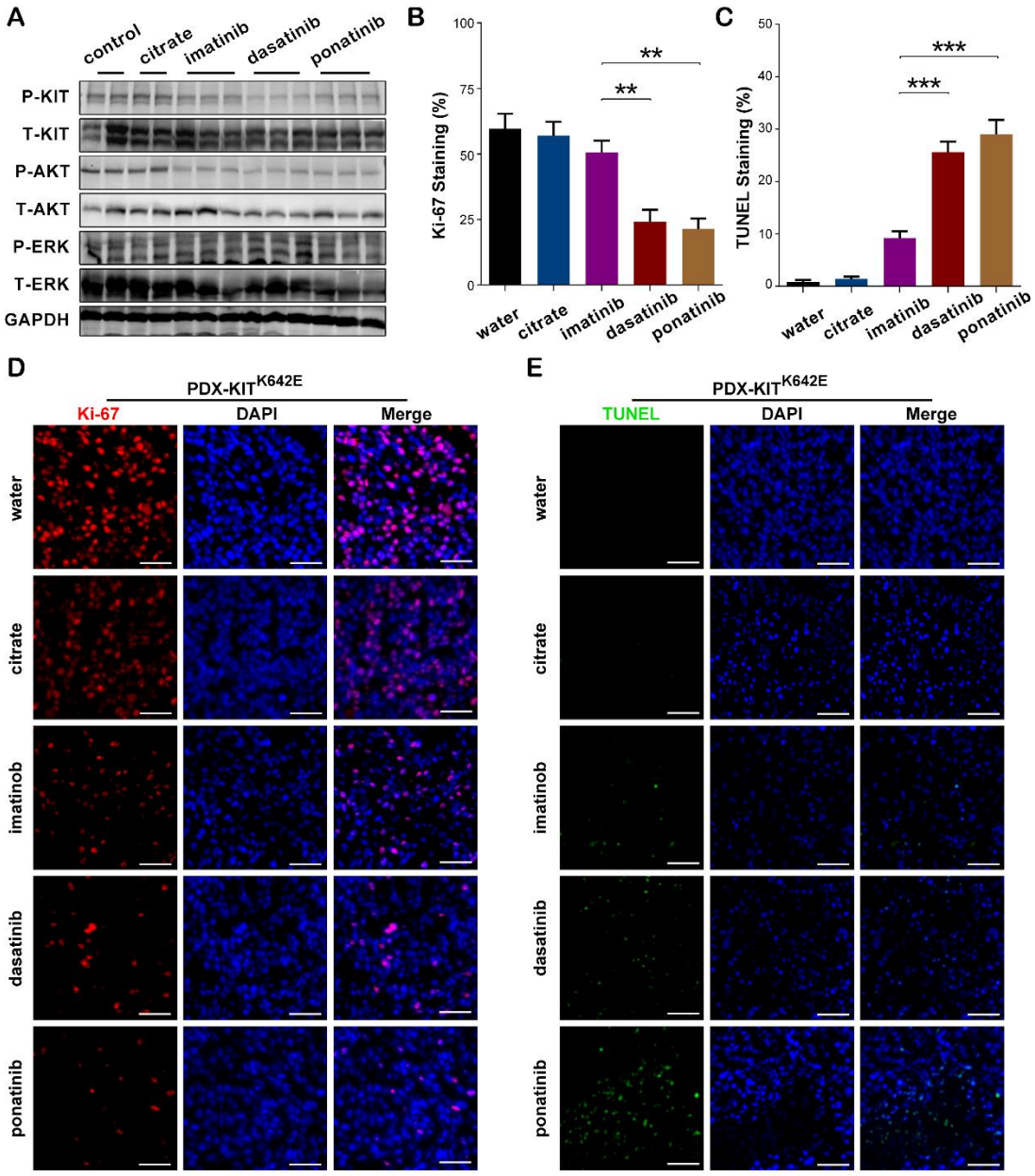


Figure S7. Inhibitory efficacy of ponatinib in PDX with *KIT*^{K642E} mutation. **(A)** Immunoblot analysis of *KIT* signaling in tumors after 28 days of treatment with imatinib, dasatinib and ponatinib. **(B)** Scoring of Ki-67 staining is summarized as the mean ± SEM. Student's *t*-test, **, $P < 0.01$. **(C)** Scoring of TUNEL staining is summarized as the mean ± SEM. Student's *t*-test, ***, $P < 0.001$. **(D)** Representative Ki-67 staining in tumors after 28 days of treatment with imatinib, dasatinib and ponatinib. Scale bar, 50μm. **(E)** Representative TUNEL staining in tumors after 28 days of treatment with imatinib, dasatinib and ponatinib. Scale bar, 50μm.

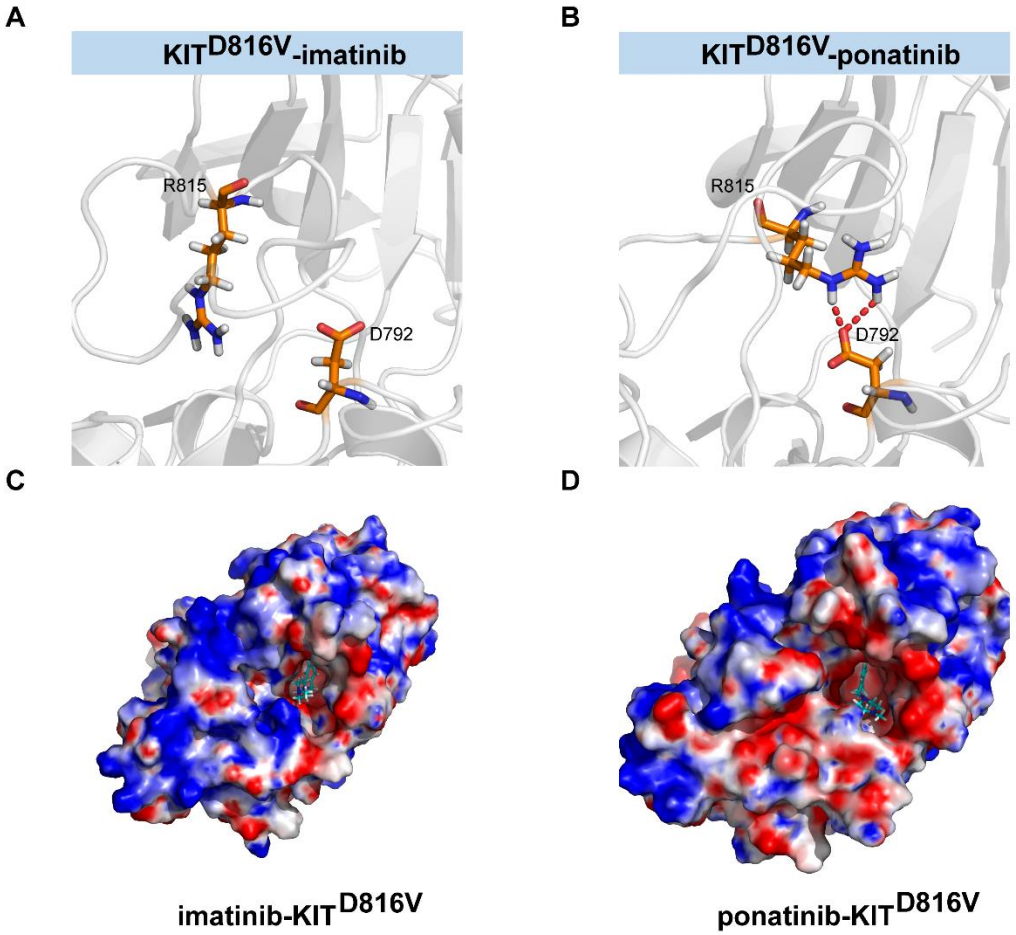


Figure S8. The salt bridge D792●●●R815 changed the distribution of the charges of the resides in the region of the ATP binding site. **(A-B)** Salt-bridges calculated over the MD simulations of imatinib/ponatinib-*KIT*^{D816V} complexes. Conformations of *KIT*^{D816V} are shown as cartoons, residues R815 and D792 are drawn in sticks, and salt-bridges are shown by dashed lines. **(C-D)** Electrostatic potential (EP) surface of the imatinib-*KIT*^{D816V} complexes. EP calculations on the Connolly solvent-accessible surfaces of the receptors were performed with the APBS software. The color scale ranges from red (electronegative potential) through white (neutral) to blue (electropositive potential).

Supplementary tables

Table S1. Summary of IC_{50} values of *KIT* inhibitors in PDCs proliferation assays.

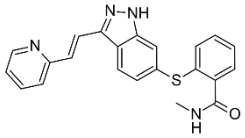
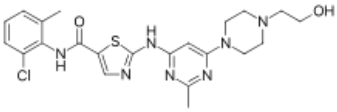
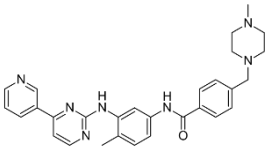
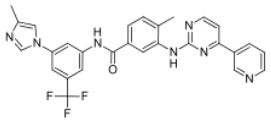
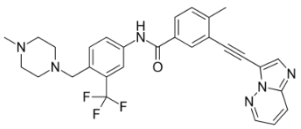
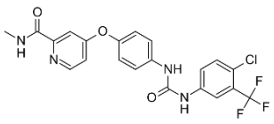
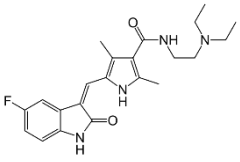
Inhibitor	*Chemical Structure*	*V560D*	*K642E*	*D816V*	*WT*
Axitinib		23.98	313.1	335.6	>10,000
Dasatinib		34.59	148.6	207.8	>10,000
Imatinib		75.66	2752	4840	>10,000
Nilotinib		58.79	1219	1891	>10,000
Ponatinib		39.05	207.6	174.3	>10,000
Sorafenib		232.4	3612	7224	>10,000
Sunitinib		1432	>10000	>10000	>10,000

Table S2. Summary of IC_{50} values of *KIT* inhibitors in Ba/F3 proliferation assays.

	Axi	*Dasa*	*Ima*	*Nilo*	*Pona*	*Sora*	*Suni*
Parent	1735.01	1868.93	>10000	>10000	2101.75	>10000	>10000
WT	59.41	28.51	39.31	267.87	7.32	159.95	136.21
V560D	283.67	88.99	221.39	1584.58	8.48	5685.08	376.28
K642E	275.04	163.91	351.36	1707.29	10.60	5003.98	195.33
D816V	704.22	467.245	572.93	3269.46	130.45	5955.37	747.65

Table S3. Summary of TGI of imatinib, dasatinib and ponatinib in *KIT*^{WT} and *KIT* mutant PDXs.

	V560D	*K642E*	*D816V*	*WT*
Imatinib	25.25	27.59	42.67	17.96
Dasatinib	68.65	81.38	67.73	33.85
Ponatinib	78.33	83.66	99.95	33.26

Table S4. Summary of free binding energy in ponatinib-*KIT*^{WT}/*KIT*^{D816V} complexes.

KIT status	*ΔG vdw*	*ΔG elect*	*ΔG sol*	*ΔG bind*
Wild Type	-76.21	-19.72	24.39	-71.54
D816V	-75.11	-26.76	26.50	-75.38