

Supplemental Data

Manuscript title: Heterogeneous binding and CNS distribution of the multi-targeted kinase inhibitor ponatinib restrict orthotopic efficacy in a patient-derived xenograft model of glioblastoma

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TABLES

Supplemental Table 1. Total and free concentrations, respective tissue-to-plasma ratios (K_p and K_{p,uu}) and distribution advantages (D_A_{total} and D_A_{free}) at 1 and 6 hours after a single oral dose (30 mg/kg) in GBM6 flank and intracranial xenograft mice. One-sample *t* test was performed to compare the experimental values of tissue partition coefficients (K_p and K_{p,uu}) with the hypothetical value of 1, and the total and free concentrations with the total (1.08 μM) and free (0.032 μM) IC₅₀ values. Data are presented as mean ± standard deviation (S.D.) (*P < 0.05).

		Flank xenograft (N = 4-6)				Intracranial xenograft (N = 3-4)		
		Plasma	Normal brain	Flank tumor	Thigh muscle	Plasma	IC tumor core	BAT
1 hour	Total concentration (μM)	1.15 ± 0.39	0.63 ± 0.20 (*)	2.98 ± 1.10 (*)	2.88 ± 1.22 (*)	1.86 ± 0.11 (*)	5.81 ± 1.85 (*)	1.08 ± 0.42
	Free concentration (nM)	2.64 ± 0.91 (*)	0.18 ± 0.058 (*)	2.62 ± 0.97 (*)	-	4.25 ± 0.26 (*)	6.82 ± 2.17 (*)	0.24 ± 0.095
	K_p	-	0.55 ± 0.086 (*)	2.58 ± 0.64 (*)	2.67 ± 1.3 (*)	-	3.11 ± 0.84 (*)	0.58 ± 0.20
	K_{p,uu}	-	0.070 ± 0.011 (*)	0.99 ± 0.24	-	-	1.59 ± 0.43 (*)	0.057 ± 0.020 (*)
	D_A_{total}	-	4.6 ± 0.45	-	-	-	-	5.5 ± 0.49
	D_A_{free}	-	13.9 ± 1.4	-	-	-	-	28.6 ± 2.6
6 hour	Total concentration	1.16 ± 0.43	1.44 ± 0.62	8.85 ± 3.88	4.71 ± 1.81	1.49 ± 0.51	5.29 ± 2.13	1.69 ± 0.34 (*)

	(μ M)			(*)	(*)		(*)	
Free concentration (nM)	2.66 ± 0.981 (*)	0.42 ± 0.179 (*)	7.78 ± 3.41 (*)	-	3.42 ± 1.16 (*)	6.20 ± 2.50 (*)	0.38 ± 0.077 (*)	
K_p	-	1.19 ± 0.23	8.78 ± 1.06 (*)	4.04 ± 0.14 (*)	-	3.62 ± 1.28 (*)	1.18 ± 0.20	
K_{p,uu}	-	0.15 ± 0.029 (*)	3.36 ± 0.41 (*)	-	-	1.86 ± 0.65 (*)	0.12 ± 0.019 (*)	
DA_{total}	-	8.1 ± 2.2	-	-	-	-	-	3.1 ± 0.97
DA_{free}	-	24.7 ± 6.7	-	-	-	-	-	16.1 ± 5.1

K_p, total tissue-to-plasma ratio

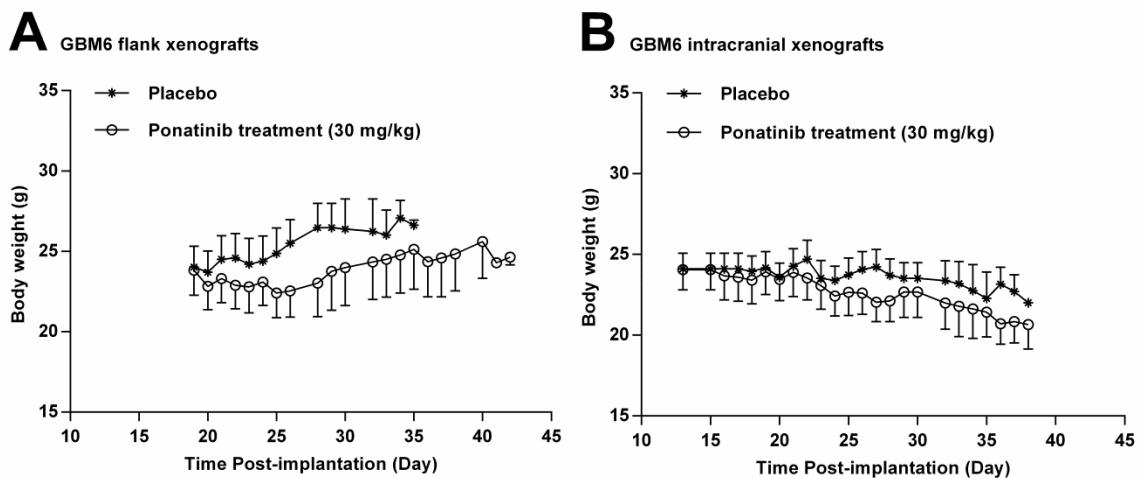
K_{p,uu}, free (unbound) tissue-to-plasma ratio

BAT, brain-around-tumor

IC tumor core, intracranial tumor core

DA_{total}, K_p,flank tumor/K_p,normal brain or K_p,IC tumor core/K_p,BAT

DA_{free}, K_{p,uu},flank tumor/K_{p,uu},normal brain or K_{p,uu},IC tumor core/K_{p,uu},BAT

Supplemental Figure 1.**LEGENDS FOR FIGURES**

Supplemental Figure 1. Trend of animal body weight in (A) GBM6 flank xenografts ($N = 9-10$) and (B) GBM6 intracranial xenografts ($N = 8-10$) following chronic administration of placebo or ponatinib (30 mg/kg)