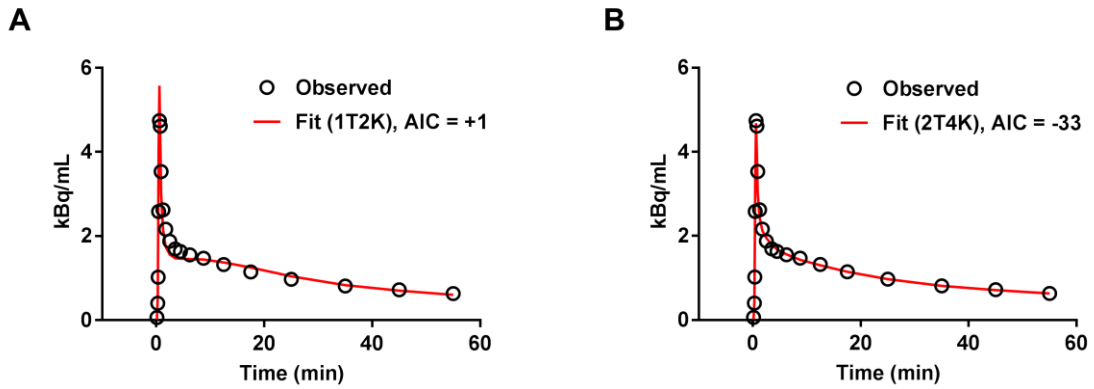
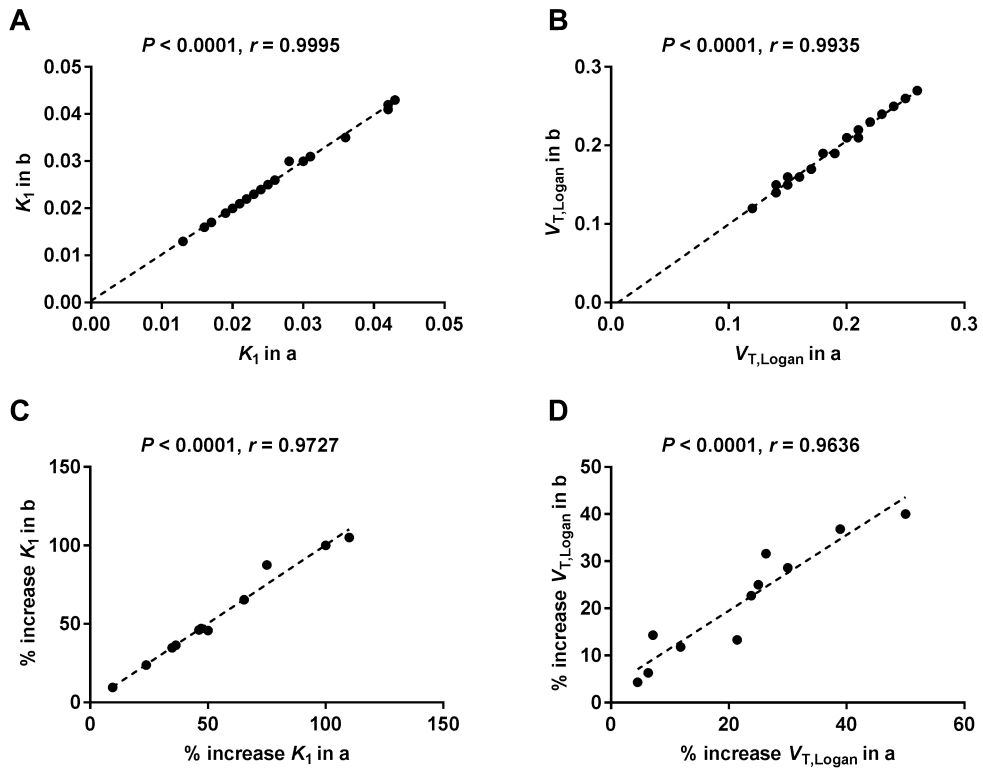
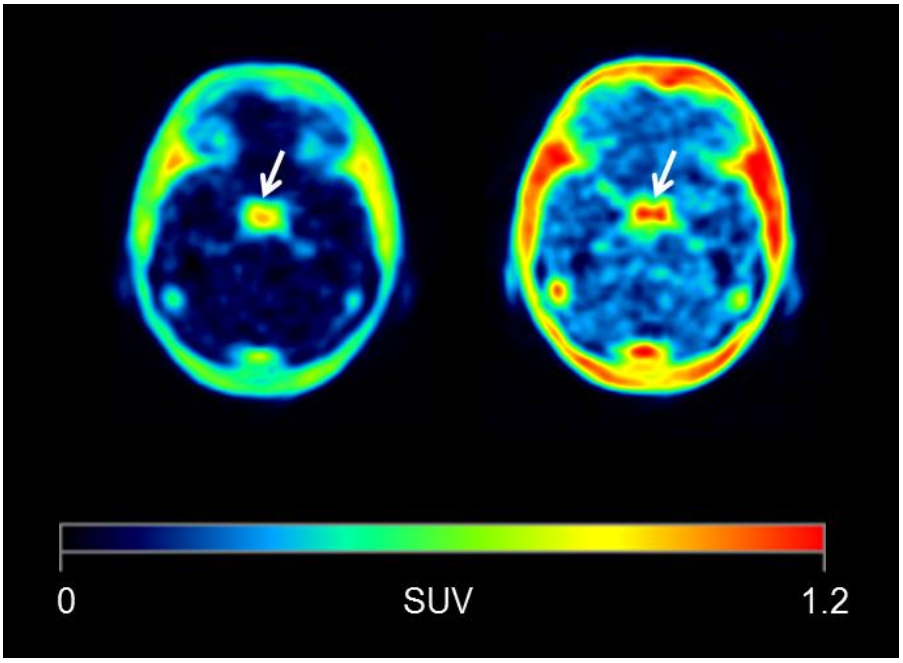


SUPPLEMENTAL FIGURE 1. Time-activity curves in whole brain gray matter for baseline scan and fits obtained with a 1-tissue-2-rate constant (1T2K, A) and a 2-tissue-4-rate constant (2T4K, B) compartment model for one representative subject (subject 06) (AIC = Akaike information criterion).



SUPPLEMENTAL FIGURE 2. Correlations between outcome parameters (K_1, $V_{T,Logan}$) determined with (in b) and without (in a) correction of radioactivity in plasma for polar radiolabeled metabolites of ^{11}C-erlotinib using the solid-phase extraction protocol (A, B). In C and D, correlations between the percentage increases in K_1 and $V_{T,Logan}$ after oral intake of unlabeled erlotinib are shown (r = Spearman correlation coefficient). Shown data are from 11 subjects pertaining to different erlotinib dose groups (300 mg: n=4, 650 mg: n=5, 1,000 mg: n=2), for whom metabolite data were available for 7 blood sampling time points.



SUPPLEMENTAL FIGURE 3. Representative transaxial PET summation images (15-60 min) for baseline scan (left image) and scan after oral intake of 650 mg erlotinib (subject 18). The pituitary gland is highlighted by a white arrow. Radioactivity concentration is normalized to injected radioactivity amount per body weight and expressed as standardized uptake value (SUV) and radiation scale is set from 0 to 1.2.

SUPPLEMENTAL TABLE 1

Adverse Events Recorded during the Study

Subject	Medication	Adverse event
01	tariquidar	hematoma, inflammation
02	tariquidar	hematoma
03	tariquidar	metallic taste, inflammation, blueish color of the fingers
04	tariquidar	inflammation, thrombosis upper arm
05	tariquidar	hypotension, chills, sweating, diarrhea, venous inflammation
06	erlotinib, 300 mg	hematoma
07	erlotinib, 300 mg	none
08	erlotinib, 300 mg	none
09	erlotinib, 300 mg	hematoma
10	erlotinib, 300 mg	none
23	erlotinib, 300 mg	hematoma, skin rash
27	erlotinib, 300 mg	hematoma
17	erlotinib, 650 mg	none
18	erlotinib, 650 mg	skin rash
19	erlotinib, 650 mg	none
20	erlotinib, 650 mg	hematoma, skin rash
21	erlotinib, 650 mg	hematoma, skin rash
22	erlotinib, 650 mg	skin rash
28	erlotinib, 650 mg	headache, hematoma, skin rash
29	erlotinib, 650 mg	skin rash
25	erlotinib, 1,000 mg	hematoma, skin rash
26	erlotinib, 1,000 mg	hematoma, skin rash

SUPPLEMENTAL TABLE 2

Percentage of Unchanged ^{11}C-Erlotinib in Plasma Determined with Solid-Phase Extraction Protocol for Baseline and Different Erlotinib Dose Groups

Time after injection	Baseline	300 mg	650 mg	1,000 mg
3.5 min	98.8±0.5	99.2±0.2	98.9±0.3	99.1±0.04
5 min	98.3±0.6	99.2±0.1	98.7±0.5	99.0±0.04
10 min	97.7±1.2	98.9±0.2	98.3±0.6	98.7±0.1
20 min	97.3±1.0	98.7±0.1	98.2±0.6	98.0±0.1
30 min	96.8±1.5	98.7±0.1	97.8±0.9	98.0±0.3
40 min	95.6±2.1	98.7±0.2	97.3±0.8	97.4±0.04
60 min	94.8±2.4	98.0±0.5	97.1±0.9	97.2±0.8

SUPPLEMENTAL TABLE 3

Pharmacokinetic Data of Unlabeled Erlotinib in Plasma

Dose	C_{max} (μmol/L)	median T_{max} (h)	AUC_{0-21} (μmol/L×h)	$AUC_{0-\infty}$ (μmol/L×h)
300 mg	5.7±2.2	3	69±15	139±57
650 mg	9.1±2.2	4	122±33	292±117
1,000 mg	8.4±1.3	2	130±5	372±2

C_{max}, maximum plasma concentration, T_{max}, time of maximum plasma concentration, AUC_{0-21}, area under the curve from 0 to 21 h after oral dosing, $AUC_{0-\infty}$, area under the curve from 0 to infinity

SUPPLEMENTAL TABLE 4

^{11}C-Erlotinib Outcome Parameters for Baseline Scan and Scan during i.v. Infusion of Tariquidar. Subjects are Grouped into their *ABCG2* Genotype

Group	Number of subjects	AUC_{brain} (SUV×min)	$V_{T,Logan}$	$V_{T,2T4K}$	K_1 (mL/(g×min))	k_2 (1/min)	k_3 (1/min)	k_4 (1/min)
c.421CC baseline	4	9.9±2.1	0.18±0.01 (1)	0.14±0.02 (4)	0.024±0.004 (11)	0.259±0.064 (15)	0.026±0.011 (39)	0.052±0.013 (32)
c.421CC tariquidar	4	14.0±3.7	0.20±0.0 (1)	0.17±0.02 (2)	0.026±0.005 (9)	0.241±0.042 (14)	0.035±0.020 (36)	0.059±0.023 (21)
c.421CA baseline	1	12.4	0.21 (1)	0.18 (1)	0.023 (5)	0.210 (8)	0.026 (14)	0.045 (8)
c.421CA tariquidar	1	17.9	0.29 (2)	0.34 (13)	0.026 (6)	0.186 (8)	0.019 (19)	0.013 (33)

Outcome parameters are given as mean ± standard deviation averaged over all subjects per group (if applicable). The value in parentheses represents the precision of parameter estimates (expressed as their coefficient of variation in percent).
AUC_{brain}, area under the brain time-activity curve; K_1, k_2, k_3, k_4, rate constants for transfer of radioactivity between the plasma, the first and the second tissue compartments calculated with 2-tissue-4-rate constant (2T4K) compartment model; $V_{T,2T4K}$, total volume of distribution calculated with 2T4K model; $V_{T,Logan}$, V_T calculated with Logan graphical analysis

SUPPLEMENTAL TABLE 5

Subjects' Genotype, Unbound Erlotinib Plasma Concentrations at the Time of the PET Scan and Whole Brain $V_{T,Logan}$ Values in Scan 1 and Scan 2

Subject ID	Dose (mg)	Genotype				C_{PET} (μM)*	V_T scan 1	V_T scan 2	Percentage change†
			ABCB1		*ABCG2*				
		rs2032582	rs1045642	rs1128503	rs2231142				
06	300	[G];[T]	[C];[T]	[C];[T]	[C];[A]	0.23 (0.22, 0.25)	0.22	0.23	+5
07	300	[G];[T]	[C];[T]	[T];[T]	[C];[A]	0.37 (0.38, 0.36)	0.14	0.21	+50
08	300	[G];[T]	[C];[T]	[C];[T]	[C];[C]	0.26 (0.28, 0.24)	0.12	0.15	+25
09	300	[G];[T]	[C];[T]	[C];[T]	[C];[C]	0.16 (0.17, 0.16)	0.16	0.17	+6
10	300	[G];[T]	[C];[T]	[T];[T]	[C];[A]	0.21 (0.22, 0.21)	0.16	0.16	+6
23	300	[T];[T]	[T];[T]	[T];[T]	[C];[C]	0.23 (0.22, 0.24)	0.18	0.21	+17
27	300	[T];[T]	[C];[T]	[C];[T]	[C];[C]	0.09 (0.09, 0.08)	0.18	0.16	-11
17	650	[G];[G]	[C];[C]	[C];[C]	[C];[C]	0.31 (0.35, 0.27)	0.14	0.15	+7
18	650	[G];[T]	[C];[T]	[C];[T]	[C];[C]	0.44 (0.44, 0.44)	0.14	0.18	+29
19	650	[G];[G]	[C];[T]	[C];[C]	[C];[A]	0.22 (0.23, 0.21)	0.19	0.24	+26
20	650	[G];[T]	[T];[T]	[C];[T]	[C];[C]	0.45 (0.44, 0.47)	0.14	0.17	+21
21	650	[G];[G]	[C];[C]	[C];[C]	[C];[C]	0.29 (0.32, 0.26)	0.17	0.19	+12
22	650	[G];[G]	[C];[T]	[C];[C]	[C];[C]	0.47 (0.45, 0.49)	0.18	0.25	+39
28	650	[G];[G]	[C];[C]	[C];[C]	[C];[A]	0.55 (0.40, 0.70)	0.18	0.20	+11
29	650	[G];[T]	[C];[T]	[C];[T]	[C];[C]	0.45 (0.35, 0.55)	0.12	0.17	+42
25	1,000	[G];[G]	[C];[T]	[C];[C]	[C];[C]	0.42 (0.46, 0.38)	0.20	0.26	+30
26	1,000	n.d.	[C];[C]	[C];[C]	[C];[C]	0.73 (0.77, 0.68)	0.21	0.26	+24

C_{PET}, unbound erlotinib plasma concentration at time of the PET scan, mean of values measured at 3 h and 4 h after oral dosing (given in parentheses); V_T, volume of distribution in whole brain gray matter calculated with Logan analysis

* in 6 out of 17 subjects no individual measurement of plasma protein binding was available, so that mean value of all other subjects was used

† percentage change in V_T in scan 2 relative to scan 1

n.d. not determined