Plasma exposure of imatinib and its correlation with clinical response in the Tyrosine Kinase Inhibitor Optimization and Selectivity Trial

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Citation: Guilhot F, Hughes TP, Cortes J, Druker BJ, Baccarani M, Gathmann I, Hayes M, Granvil C, and Wang Y. Plasma exposure of imatinib and its correlation with clinical response in the Tyrosine Kinase Inhibitor Optimization and Selectivity Trial. Haematologica 2012;97(5):731-738. doi:10.3324/haematol.2011.045666

Online Supplementary Table S1. Actual dose intensity by month. *Dose intensity (total amount of drug received divided by the number of days on treatment, including days of zero dose) up to the specified month.

	Dose															
	400 mg/day arm (n=157)								800 mg/day arm (n=316)							
	Month*								Month*							
	1	2	3	4	5	6	9	12	1	2	3	4	5	6	9	12
Dose intensity*, n (%)																
0 - <200 mg/day	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (1)	1 (<1)	1 (<1)	0	0	2 (<1)	2 (<1)	2 (<1)	1 (<1)	2 (<1)	0
200 - <400 mg/day	30 (19)	44 (28)	49 (31)	53 (34)	56 (36)	59 (38)	64 (41)	68 (43)	10 (3)	16 (5)	15 (5)	14 (4)	15 (5)	17 (5)	15 (5)	21 (7)
400 - <600 mg/day	126 (80)	112 (71)	107 (68)	103 (66)	100 (64)	96 (61)	92 (59)	88 (56)	69 (22)	67 (21)	74 (23)	76 (24)	80 (25)	77 (24)	81 (26)	81 (26)
600 - <800 mg/day	0	0	0	0	0	0	0	0	97 (31)	123 (39)	133 (42)	142 (45)	140 (44)	148 (47)	153 (48)	152 (48)
≥800 mg/day	0	0	0	0	0	0	0	0	140 (44)	110 (35)	92 (29)	82 (26)	79 (25)	73 (23)	65 (21)	62 (20)

Online Supplementary Table S2. Summary of Cmin levels of imatinib and CGP74588 and their ratios over the actual imatinib dose administered at months 1 (day 29), 6, 9, and 12 (pooled analysis of patients from both arms).

			Imatinib (ng/mL)				CGP74588 (ng/mL)				CGP74588/Imatinib ratio			
Month	Dose* (mg/day)	n	**Median**	Mean	SD	CV%	**Median**	Mean	SD	CV%	**Median**	Mean	SD	CV%
1	300	0	-	-	-	-	-	-	-	-	-	-	-	-
	400	97	1230	1609	1089	68%	301	356	203	57%	0.22	0.25	0.09	38%
	600	7	1980	1711	1433	84%	282	324	260	80%	0.17	0.21	0.09	42%
	800	119	2720	2928	1426	49%	485	564	296	52%	0.19	0.20	0.06	31%
6	300	10	713	731	558	76%	173	160	93	58%	0.24	0.24	0.07	29%
	400	97	1100	1222	673	55%	239	263	116	44%	0.23	0.26	0.27	103%
	600	34	1765	1910	1171	61%	290	367	186	51%	0.20	0.28	0.33	117%
	800	105	2760	2820	1255	45%	494	540	271	50%	0.19	0.20	0.05	26%
9	300	9	911	1253	1192	95%	251	240	81	34%	0.26	0.24	0.07	31%
	400	97	1230	1394	740	53%	278	285	101	35%	0.21	0.28	0.30	107%
	600	24	2155	2057	948	46%	354	391	179	46%	0.20	0.21	0.07	35%
	800	92	2455	2570	1266	49%	467	491	241	49%	0.19	0.24	0.29	124%
12	300	12	1625	1675	695	41%	288	294	92	31%	0.19	0.19	0.07	35%
	400	101	1260	1471	1065	72%	277	303	189	62%	0.21	0.23	0.10	43%
	600	25	1650	1901	956	50%	324	363	169	46%	0.21	0.22	0.10	46%
	800	95	2710	2568	1188	46%	474	480	239	50%	0.19	0.19	0.05	27%
Total	300	31	**1040**	1248	901	72%	**248**	235	103	44%	**0.22**	0.22	0.07	33%
	400	395	**1200**	1425	919	64%	**268**	301	162	54%	**0.22**	0.25	0.21	83%
	600	90	**1935**	1931	1065	55%	**322**	369	183	50%	**0.21**	0.24	0.22	90%
	800	411	**2690**	2737	1299	47%	**482**	522	266	51%	**0.19**	0.21	0.15	72%

*CV: coefficient of variation; SD: standard deviation. *Doses with too few Cmin values (n<5, for 200 mg or 500 mg) are not included.*

Online Supplementary Table S3. Summary of imatinib Cmin at day 29 by race and by dose.

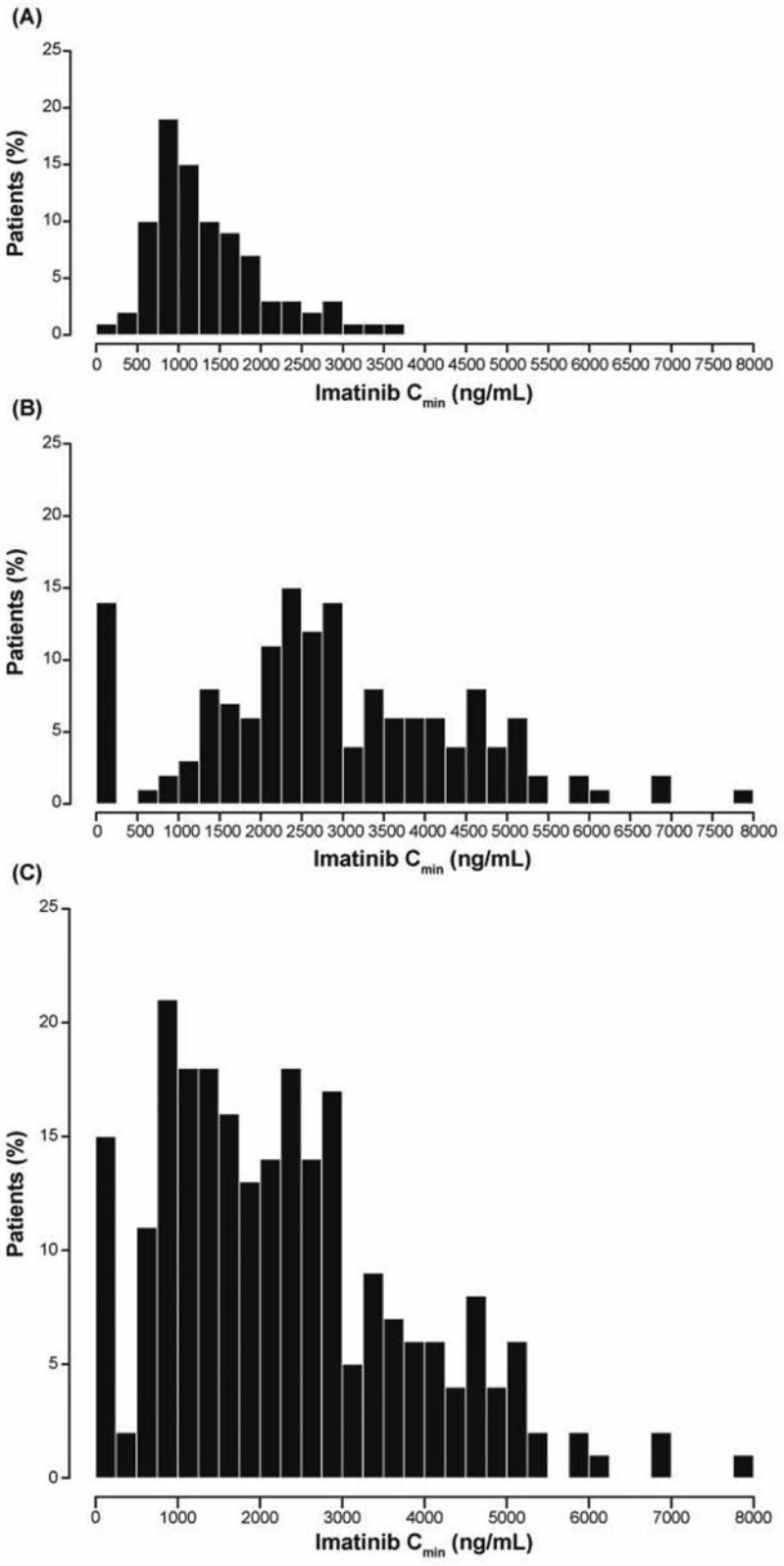
Imatinib dose, mg/day	Race	Median imatinib C_{min}, ng/mL (25th-75th percentile)	Median CGP74588/imatinib C_{min} Ratio (25th-75th percentile)
400 (n=87)	White (n=54)	1225 (888-1660)	0.224 (0.196-0.298)
	Asian (n=19)	1120 (765-1710)	0.229 (0.206-0.267)
	Other/unknown (n=14)	1395 (881-2040)	0.225 (0.196-0.253)
800 (n=153)	White (n=108)	2695 (1930-3725)	0.200 (0.160-0.241)
	Asian (n=34)	2770 (1400-4080)	0.173 (0.150-0.214)
	Other/unknown (n=11)	2900 (1490-4930)	0.215 (0.167-0.233)
Both arms combined (n=240)	White (n=162)	NA	0.208 (0.167-0.249)
	Asian (n=53)	NA	0.206 (0.171-0.236)
	Other/unknown (n=25)	NA	0.217 (0.185-0.239)

NA: not applicable.

Online Supplementary Table S4. Summary of imatinib Cmin at day 29 by Sokal risk score and by dose.

PK parameters	Sokal risk group		
	Low	Intermediate	High
400 mg/day arm (n=87)	n=34	n=31	n=22
Median imatinib C_{min}, ng/mL (25th-75th percentile)	1175 (919-1550)	1450 (851-1930)	1050 (812-1660)
Median CGP74588/imatinib C_{min} ratio (25th-75th percentile)	0.237 (0.196-0.304)	0.218 (0.196-0.249)	0.234 (0.205-0.290)
800 mg/day arm (n=153)	n=67	n=47	n=39
Median imatinib C_{min}, ng/mL (25th-75th percentile)	2890 (2040-4120)	2700 (1720-3810)	2430 (1740-3730)
Median CGP74588/imatinib C_{min} ratio (25th-75th percentile)	0.201 (0.161-0.240)	0.178 (0.151-0.219)	0.205 (0.160-0.242)
Both arms combined (n=240)	n=101	n=78	n=61
Median CGP74588/imatinib C_{min} ratio (25th-75th percentile)	0.211 (0.171-0.247)	0.205 (0.162-0.225)	0.213 (0.180-0.263)
Imatinib C_{min} quartiles, n (%)	n=101	n=78	n=61
<1165 ng/mL (n=60)	26 (25.7)	18 (23.1)	16 (26.2)
1165-3180 ng/mL (n=120)	48 (47.5)	40 (51.3)	32 (52.5)
>3180 ng/mL (n=60)	27 (26.7)	20 (25.6)	13 (21.3)

Online Supplementary Figure S1. Distribution of imatinib C_{min} (ng/mL) at 400 mg daily (n=87) (A), 800 mg daily (n=153) (B), and from both arms pooled together (n=240) (C) at steady state on day 29.



Online Supplementary Figure S2. Time to MMR by imatinib Cmin at day 29 (pooled analysis of patients from both arms; Kaplan-Meier analyses) in patients with low risk (n=101) (A), intermediate risk (n=78) (B), and high risk (n=61) (C) Sokal scores. Patients without MMR were censored at last assessment on study treatment.