

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006;354:2531-41.

Supplemental Table 1: Definitions of Hematologic Resistance

I. Primary Resistance

a) Chronic phase

- 1) Fail to achieve a CHR with 400 mg/day of imatinib for at least 3 months **or**
- 2) WBC $\geq 10,000/\text{mm}^3$ and rising on 2 consecutive measurements at least 14 days apart with at least one measurement demonstrating WBC $> 15,000/\text{mm}^3$ while on imatinib 400 mg/day

b) Advanced phase

- 1) Fail to achieve a major or minor hematologic response after 3 months of imatinib treatment

II. Acquired Resistance

a) Chronic phase

- 1) Achieve a CHR **and**
- 2) Develop a rising WBC $\geq 10,000/\text{mm}^3$ and rising on 2 consecutive measurements at least 14 days apart with at least one measurement demonstrating WBC $> 15,000/\text{mm}^3$

b) Advanced phase

- 1) Achieve a major or minor hematologic response with imatinib and then progress
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Supplemental Table 2: Hematologic Response Criteria

I. Chronic Phase CML

a) Complete Hematologic Response (CHR)

- 1) WBC \leq institutional ULN
- 2) Platelets $< 450,000/\text{mm}^3$
- 3) No blasts or promyelocytes in peripheral blood
- 4) $< 5\%$ myelocytes plus metamyelocytes in peripheral blood
- 5) Basophils in peripheral blood $< 20\%$
- 6) No extramedullary involvement (including no hepatomegaly or splenomegaly)

II. Accelerated and Blast Phase CML and Ph+ ALL

a) Major Hematologic Response (Major HR)

1. Complete Hematologic Response (CHR)

- 1) WBC \leq institutional ULN
- 2) ANC $\geq 1000/\text{mm}^3$
- 3) Platelets $\geq 100,000/\text{mm}^3$
- 4) No blasts or promyelocytes in peripheral blood
- 5) Bone marrow blasts $\leq 5\%$
- 6) $< 5\%$ myelocytes plus metamyelocytes in peripheral blood
- 7) Basophils in peripheral blood $< 20\%$
- 8) No extramedullary involvement (including no hepatomegaly or splenomegaly)

2. No Evidence of Leukemia (NEL)

- 1) WBC \leq institutional ULN
- 2) No blasts or promyelocytes in peripheral blood
- 3) Bone marrow blasts $\leq 5\%$
- 4) $< 5\%$ myelocytes plus metamyelocytes in peripheral blood
- 5) Basophils in peripheral blood $< 20\%$
- 6) No extramedullary involvement (including no hepatomegaly or splenomegaly)
- 7) At least one of the following : (i) $20,000/\text{mm}^3 \leq \text{Platelets} < 100,000/\text{mm}^3$; (ii) $500/\text{mm}^3 \leq \text{ANC} < 1000/\text{mm}^3$

b) Minor Hematologic Response (Minor HR)

- 1) $< 15\%$ blasts in bone marrow and in peripheral blood
 - 2) $< 30\%$ blasts plus promyelocytes in bone marrow and peripheral blood
 - 3) $< 20\%$ basophils in peripheral blood
 - 4) No extramedullary involvement other than spleen and liver
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Supplemental Table 3 - Summary of Dasatinib Treatment Responses, Prior Imatinib Response and Bcr/Abl Genotype in Chronic Phase Patients

Patient Number	Reason for imatinib discontinuation	Best Cytogenetic Response on Imatinib	Best Hematologic Response on Dasatinib	Best Cytogenetic Response on Dasatinib	Pretreatment Mutation(s) (Number of Clones positive/Total Clones Examined)
CP-1	intolerant	CCyR	CHR	CCyR	None
CP-2	resistant	partial	CHR	CCyR	F486S 2/11
CP-3	resistant	minor	CHR	CCyR	G250E 3/10 F359C 5/10
CP-4	resistant	partial	CHR	CCyR	M351T 11/11
CP-5	resistant	CCyR	none	none	E255V 1/10
CP-6	resistant	none	CHR	none	H396R 9/11 E355G 1/11
CP-7	resistant	CCyR	CHR	CCyR	E98G 11/11
CP-8	intolerant	partial	CHR	none	G250E 1/12 H396R 1/12 E355G 1/12 F486S 1/12
CP-9	intolerant	partial	CHR	CCyR	None
CP-10	resistant	none	CHR	none	M351T 3/11 F486S 3/11 D444G 2/11 E450G 1/11
CP-11	resistant	minimal	CHR	minimal	E255K 12/12
CP-12	resistant	none	CHR	none	Y253H 4/10 M388L 5/10 M388L/M244V 1/10
CP-13	resistant	none	CHR	minimal	E355G 8/10 E355G/Q252R 1/10
CP-14	resistant	none	CHR	none	L364I 9/12
CP-15	resistant	partial	CHR	CCyR	E450Q/M351T 1/10 E450Q 9/10

CP-16	resistant	none	CHR	none	F317L 1/12 V90A/S157R/Y174C/K400E 2/12
CP-17	resistant	partial	CHR	CCyR	M351T 8/9 M351S 1/9
CP-18	resistant	none	CHR	none	None
CP-19	intolerant	CCyR	CHR	CCyR	L323P 2/12 I403V/T 1/12, 1/12 V379I 1/12
CP-20	resistant	minimal	CHR	minimal	V289I 8/11 V289I/M388L 1/11 G250E 1/11
CP-21	resistant	CCyR	CHR	CCyR	Y253H 11/11
CP-22	resistant	none	CHR	none	E255V 6/10 E255V/Q447R 2/10 E255V/T345A 1/10 E255V/T345A/H396R 1/10
CP-23	intolerant	none	CHR	minimal	F359C 1/10
CP-24	resistant	minor	CHR	partial	G250E 10/10
CP-25	resistant	none	CHR	none	M244V 12/12
CP-26	resistant	none	CHR	none	E255V 10/11 E255K 1/11
CP-27	resistant	none	none	none	T315I 2/10 F359V 6/10 M244V 1/10 G250E 1/10
CP-28	resistant	none	CHR	partial	M351T 4/10
CP-29	resistant	partial	CHR	CCyR	M351T 10/10
CP-30	resistant	none	none	none	S438C 6/10 K466E/R 1/10, 1/10
CP-31	resistant	partial	CHR	minimal	None
CP-32	intolerant	CCyR	CHR	CCyR	None
CP-33	resistant	none	CHR	none	F359I 9/9
CP-34	resistant	none	CHR	minimal	V186A 2/12

CP-35	resistant	none	CHR	minimal	L387M 7/10 L387M / F192L 2/10 E450G 1/10
CP-36	resistant	partial	CHR	CCyR	D363G 2/10
CP-37	resistant	none	CHR	none	F359V 6/10 F359V/F486S 1/10 F359V/L273M 2/10 L273M 1/10
CP-38	intolerant	n/a	CHR	partial	None
CP-39	intolerant	partial	CHR	CCyR	None
CP-40	resistant	n/a	CHR	partial	G250E 9/10 G250E/F317L 1/10

Mutations were detected by sequencing 10 or more independent clones as described in methods and listed only if present in at least 2 of 10 clones or if previously reported in imatinib-resistant patients. Color code: pink (reported previously in patients), brown (mutation at this position reported previously but with different amino acid substitution), aqua (not reported previously, but found in multiple clones of the same patient in this trial). Patients off study are highlighted in grey.

Supplemental Table 4 - Summary of Dasatinib Treatment Responses and Bcr/Abl Genotype in Advanced Phase Patients

Patient Number	Reason for imatinib discontinuation	Best Hematologic Response on Dasatinib	Best Cytogenetic Response on Dasatinib	Pretreatment Mutations Number of Clones positive/Total Clones Examined
AP-1	resistant	CHR	none	None
AP-2	resistant	CHR	none	M351T 6/10 M351A 1/10
AP-3	resistant	none	none	T315I 8/10
AP-4	resistant	CHR	CCyR	G250E 5/8 G250E/E450G 1/8 G250E/E453G 1/8
AP-5	intolerant	NEL	minimal	Y253H 1/11
AP-6	intolerant	NEL	none	None
AP-7	resistant	CHR	partial	None
AP-8	resistant	none	none	T315I 10/10
AP-9	resistant	NEL	none	E355G 6/10 E355G/L324Q 1/10 L324Q 3/10
AP-10	resistant	NEL	CCyR	E279K 3/11 V379I 5/11 V379I/F317L/M351T 1/11
AP-11	resistant	CHR	none	G250E/E138G/I242T/K271R/V338M 3/12 G250E/E138G/I242T/K271R 1/12 G250E/I242T/K271R/V338M/N146S 1/12 N146S another 7/12
MBC-1	resistant	CHR	minor	None
MBC-2	resistant	CHR	none	V379I 9/10
MBC-3	resistant	CHR	CCyR	None
MBC-4	resistant	none	none	M244V 1/11
MBC-5	resistant	CHR	CCyR	M351T 10/10
MBC-6	resistant	NEL	none	None
MBC-7	resistant	CHR	CCyR	G250E 1/10 D276G 1/10
MBC-8	resistant	CHR	CCyR	None

MBC-9	resistant	minor	minimal	G250E 11/11
MBC-10	resistant	minor	none	None
MBC-11	resistant	none	none	F486S 1/11
MBC-12	intolerant	NEL	none	None
MBC-13	resistant	none	none	F359V 1/10
MBC-14	resistant	minor	none	E255V 10/12 E292V 2/12
MBC-15	resistant	NEL	CCyR	F359V 9/12 F359V/Q252R 1/12 L273M 2/12
MBC-16	resistant	minor	minor	None
MBC-17	resistant	CHR	CCyR	N49S 2/11
MBC-18	resistant	CHR	partial	G250E 8/11 G250E/S126P 2/12 G250E/F486S 1/12
MBC-19	resistant	NEL	none	M244V/L364I 5/11 M244V/L364I/N53S 2/11 M244V/L364I/M458T 1/11 L364I/M458T 1/11 L364I 2/11
MBC-20	resistant	NEL	minimal	None
MBC-21	resistant	NEL	partial	None
MBC-22	resistant	none	none	F359V 9/10
MBC-23	resistant	none	none	None
LBC-1	resistant	CHR	partial	C100R 2/10 F486S 1/10
LBC-2	resistant	CHR	partial	E355G 10/10
LBC-3	resistant	CHR	partial	None
LBC-4	resistant	CHR	CCyR	None
LBC-5	intolerant	CHR	CCyR	None
ALL-1	resistant	none	partial	Y253H 3/11 insert RN at 293-294 8/11
ALL-2	resistant	CHR	partial	M244V 1/11
ALL-3	resistant	CHR	CCyR	Y253H 9/10 Y253H/Q252R 1/10
ALL-4	resistant	none	none	E255K 3/12
ALL-5	resistant	NEL	minor	None

Mutations were detected by sequencing 10 or more independent clones as described in methods and listed only if present in at least 2 of 10 clones or if previously reported in imatinib-resistant patients. Color code: pink (reported previously in patients), brown (mutation at this position reported previously but with different amino acid substitution), aqua (not reported previously, but found in multiple clones of the same patient in this trial). Patients off study are highlighted in grey.

Supplemental Table 5: Baseline Hematologic Parameters Prior to Dasatinib Treatment

	Grade 3				Grade 4			
	CP	AP	MBC	LBC/Ph+	CP	AP-CML	MBC	LBC/Ph+
	(N=40)	(N=11)	(N=23)	ALL (N=10)	(N=40)	(N=11)	(N=23)	ALL (N=10)
ANC	0	1 (9)	3 (13)	1 (10)	0	1 (9)	4 (17)	1 (10)
Platelets	0	1 (9)	7 (30)	5 (50)	0	2 (18)	7 (30)	2 (20)
Hgb	2 (5)	0	6 (26)	0	1 (3)	0	0	0

Supplemental Table 6: Dose Modifications

	CP CML	AP CML	MBC-CML	LBC-CML/	Total
	N=40	n=11	n=23	ALL n=10	N=84
Interruptions	29 (73)	7 (64)	12 (52)	3 (30)	53 (63)
Reductions	12 (30)	3 (27)	5 (22)	1 (10)	21 (25)
Escalations	18 (45)	1 (9)	2 (9)	1 (10)	20 (24)

Supplemental Table 7: Laboratory Abnormalities Regardless of Relationship to Treatment

	Grade 1-4				Grade 3-4			
			LBC/				LBC/	
	CP (N=40)	AP (N=11)	MBC (N=23)	ALL (N=10)	CP (N=40)	AP (N=11)	MBC (N=23)	ALL (N=10)
Elevated AST	23 (56)	7 (64)	13 (57)	9 (90)	1 (3)	0	2 (9)	0
Elevated ALT	15 (38)	8 (73)	13 (57)	7 (70)	0	1 (9)	2 (9)	0
Elevated Total bilirubin	3 (8)	2 (18)	10 (43)	5 (50)	1 (3)	0	4 (17)	0
Elevated creatinine	14 (35)	2 (18)	12 (52)	6 (60)	0	0	0	0
Hypocalcemia	26 (65)	8 (73)	21 (91)	7 (70)	3 (8)	2 (18)	6 (26)	3 (30)
Hypomagnesemia	13 (33)	5 (45)	26 (70)	3 (30)	1 (3)	0	1 (4)	0

Supplemental Table 8: Dose at Time of Response

Starting Dose Level	CHR/MHR		MCyR	
	Number of Responses at Starting Dose*	Number of Responses at Escalated Dose	Number of Responses at Starting Dose*	Number of Responses at Escalated Dose
Chronic Phase QD Dosing (N=21)				
15 mg QD	1/3	2/2	0	3/3
30 mg QD	1/3	1/2	0	1/3
50 mg QD	3/3	-	2/3	0/3
75 mg QD	1/3	2/2	0/3	0/3
105 mg QD	2/3	1/1	1/3	0/2
140 mg QD	3/3	-	1/3	0/2
180 mg QD	3/3	-	2/3	-
Chronic Phase BID Dosing (N=19)				
25 mg BID	2/3	1/1	0	1/3
35 mg BID	5/7	0/2	1/7	1/6
50 mg BID	3/3	-	1/3	-
70 mg BID	6/6	-	4/6	-
Advanced Phase BID Dosing (N=44)				
35 mg BID	1/1	-	1/1	-
50 mg BID	5/8	-	2/8	-
70 mg BID	15/17	-	10/17	-
90 mg BID	7/11	-	5/11	-
120 mg BID	3/7	-	1/7	-

* Nine patients who were reduced below their starting dose were counted as responding at the initial starting dose (includes 2 chronic QD, 1 chronic BID, and 1 advanced phase patient for CHR/MHR and 1 chronic QD and 4 advanced phase patients for MCyR)