

## Phase III, Randomized, Open-Label Study of Daily Imatinib Mesylate 400 mg Versus 800 mg in Patients With Newly Diagnosed, Previously Untreated Chronic Myeloid Leukemia in Chronic Phase Using Molecular End Points: Tyrosine Kinase Inhibitor Optimization and Selectivity Study

Jorge E. Cortes, Michele Baccarani, François Guilhot, Brian J. Druker, Susan Branford, Dong-Wook Kim, Fabrizio Pane, Ricardo Pasquini, Stuart L. Goldberg, Matt Kalaycio, Beatriz Moiraghi, Jacob M. Rowe, Elena Tothova, Carmino De Souza, Marc Rudoltz, Richard Yu, Tillmann Krahnke, Hagop M. Kantarjian, Jerald P. Radich, and Timothy P. Hughes

From The University of Texas M. D. Anderson Cancer Center, Houston, TX; University of Bologna, Instituto de Emotologia L. e A. Seràgnoli, Bologna; University of Naples, Naples, Italy; Clinical Investigation Centre 802 INSERM, CHU de Poitiers, Poitiers, France; Oregon Health Sciences University Knight Cancer Institute, Portland, OR; SA Pathology, Royal Adelaide Hospital, Adelaide, Australia; Seoul St Mary's Hospital, Catholic University of Korea, Seoul, Korea; Hospital De Clinicas De Curitiba, Parana; Hospital de Clinicas da UNICAMP, Campinas, Brazil; The Cancer Center, Hackensack University Medical Center, Hackensack; Novartis Pharmaceuticals, East Hanover, NJ; Cleveland Clinic Foundation, Cleveland, OH; Hospital Jose Maria Ramos Mejia, Buenos Aires, Argentina; Rambam Medical Center, Haifa, Israel; Hospital University of PJS, Kosice, Slovakia; Novartis Pharma AG, Basel, Switzerland; and Fred Hutchinson Cancer Research Center, Seattle, WA.

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Corresponding author: Jorge E. Cortes, MD, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, 4th Floor, Rm 3000, Box 0428, Houston, TX 77030; e-mail: [Jcortes@mdanderson.org](mailto:Jcortes@mdanderson.org).

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### A B S T R A C T

#### Purpose

To evaluate the safety and efficacy of initial treatment with imatinib mesylate 800 mg/d (400 mg twice daily) versus 400 mg/d in patients with newly diagnosed chronic myeloid leukemia in chronic phase.

#### Patients and Methods

A total of 476 patients were randomly assigned 2:1 to imatinib 800 mg ( $n = 319$ ) or 400 mg ( $n = 157$ ) daily. The primary end point was the major molecular response (MMR) rate at 12 months.

#### Results

At 12 months, differences in MMR and complete cytogenetic response (CCyR) rates were not statistically significant (MMR, 46% v 40%;  $P = .2035$ ; CCyR, 70% v 66%;  $P = .3470$ ). However, MMR occurred faster among patients randomly assigned to imatinib 800 mg/d, who had higher rates of MMR at 3 and 6 months compared with those in the imatinib 400-mg/d arm ( $P = .0035$  by log-rank test). CCyR also occurred faster in the 800-mg/d arm (CCyR at 6 months, 57% v 45%;  $P = .0146$ ). The most common adverse events were edema, gastrointestinal problems, and rash, and all were more common in patients in the 800-mg/d arm. Grades 3 to 4 hematologic toxicity also occurred more frequently in patients receiving imatinib 800 mg/d.

#### Conclusion

MMR rates at 1 year were similar with imatinib 800 mg/d and 400 mg/d, but MMR and CCyR occurred earlier in patients treated with 800 mg/d. Continued follow-up is needed to determine the clinical significance of earlier responses on high-dose imatinib.

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### INTRODUCTION

Imatinib mesylate (ie, imatinib) is the currently approved first-line treatment for chronic myeloid leukemia (CML).<sup>1,2</sup> Seven-year data from the phase III International Randomized Study of Interferon and STI571 (IRIS), which compared imatinib with interferon- $\alpha$  plus cytarabine, demonstrated a cumulative best complete cytogenetic response (CCyR) rate of 82% in patients randomly assigned to imatinib.<sup>3</sup> At 7 years, freedom from progression to accelerated phase/blast crisis (AP/BC) was 93%, and overall survival (OS) was

86%.<sup>3</sup> Achievement of MMR on imatinib is predictive of long-term event-free and transformation-free survivals.<sup>4-8</sup>

The recommended starting doses of imatinib are 400 mg/d for patients with CML in chronic phase (CML-CP) and 600 mg/d for patients in AP or BC. Despite high response rates with imatinib at 400 mg/d, data from nonrandomized studies suggest that initial therapy with imatinib 800 mg/d might lead to higher CCyR and major molecular response (MMR) rates and that these responses might occur faster than with the standard 400 mg/d dose in patients with CML-CP.<sup>9-13</sup>

A phase III, randomized study was conducted to evaluate whether treatment with imatinib 800 mg/d improves outcomes compared with imatinib 400 mg/d in patients with newly diagnosed, previously untreated, Philadelphia chromosome-positive (Ph+) CML-CP, and the rate of MMR at 12 months was the primary end point.

**PATIENTS AND METHODS**

Inclusion criteria, response definitions, and a detailed description of molecular assessments are provided in the data supplement (online only). Patients with newly diagnosed, Ph+ CML-CP between the ages of 18 and 75 years were eligible. All patients were enrolled within 6 months of diagnosis. Patients had no prior treatment for CML (except hydroxyurea, anagrelide, or ≤ 2 weeks of prior imatinib; Fig 1).

**Trial Design**

In this phase III, open-label, randomized, multicenter study, patients were randomly assigned 2:1 to imatinib 800 mg (400 mg twice daily) or 400 mg (once daily). Patients were stratified according to Sokal score at diagnosis.<sup>14</sup>

Complete blood counts were measured at baseline; at weeks 1, 2, and 4 monthly until month 6; and every 3 months thereafter until the end of the study. Conventional bone marrow cytogenetics were performed at baseline, at months 6 and 12, and every 6 months until CCyR was achieved. Molecular response was assessed by real-time, quantitative, reverse transcriptase poly-

merase chain reaction (RQ-PCR) at baseline, then monthly for 3 months, then every 3 months.

Patients were allowed to discontinue treatment in cases of progression or intolerance. In the absence of dose-limiting adverse events, patients in the imatinib 400-mg/d arm were allowed to escalate the dose to 800 mg/d if the following criteria for response failure were met: no complete hematologic response (CHR) by 3 months, no or minimal cytogenetic response (ie, > 65% Ph+ metaphases in bone marrow) by 6 months, or no CCyR (ie, ≥ 1% Ph+ metaphases in bone marrow) by 12 months. Patients in the 800-mg/d arm were not permitted to escalate the dose. Dose reductions were allowed for grades 3 to 4 toxicity or for persistent grade 2 toxicity.

**End Points**

The primary end point of this study was the rate of MMR at 12 months, defined as a *BCR-ABL*:control gene ratio ≤ 0.1% by RQ-PCR in peripheral blood expressed on the international scale.<sup>15-17</sup> Four regional laboratories were used to perform molecular analyses. Month-12 samples also were forwarded to the Institute of Medical and Veterinary Science (Adelaide, Australia) for central evaluation. If no 12-month PCR data were available and if results from both months 9 and 15 indicated MMR, patients were classified as having achieved MMR. Imputation of outcome was possible for 11 patients, which resulted in five additional imputed responses for the primary end point. The patient was classified as a nonresponder if no data were available at 12 months.

Secondary objectives included time to MMR, rate of CCyR, time to CCyR, progression-free survival (PFS, defined as progression to AP/BC or death as a result of any cause while on study treatment), OS, safety, and actual

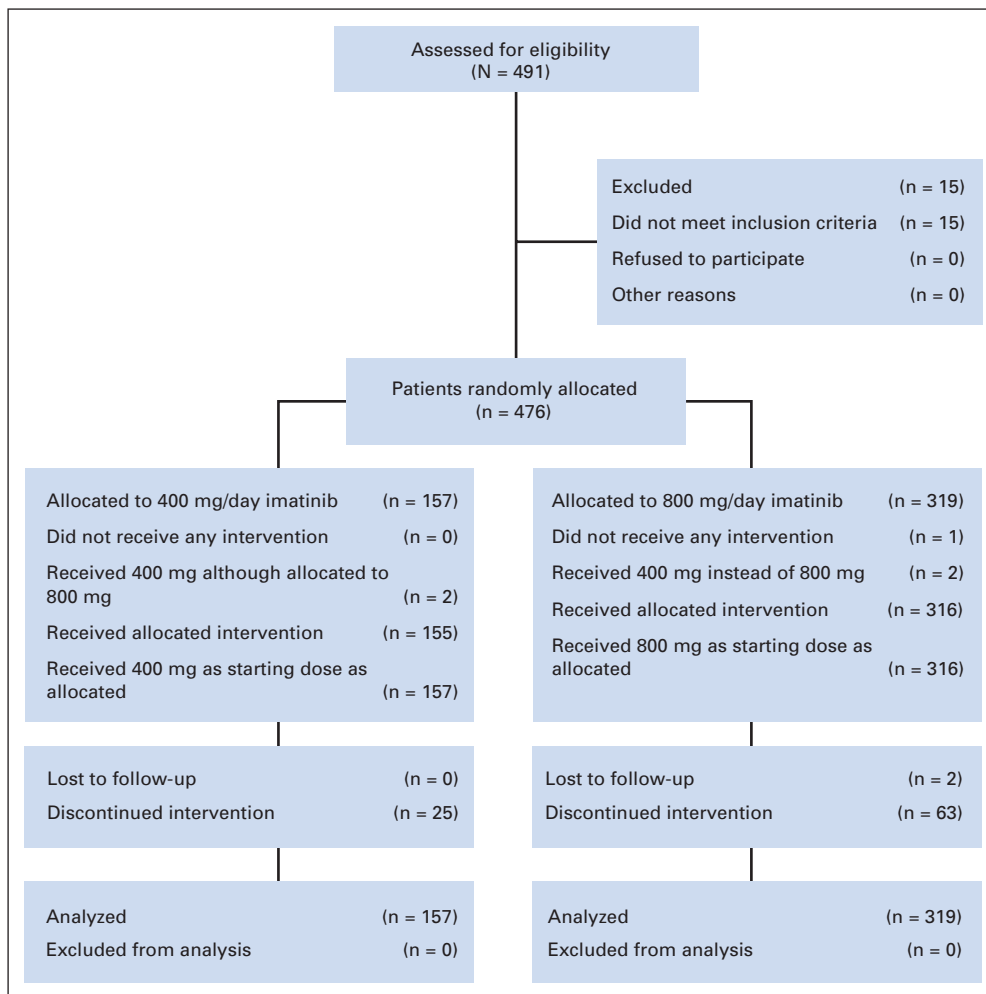


Fig 1. CONSORT diagram.

dose intensity delivered in each arm. Events were defined as the first occurrence of any of the following on study treatment: death as a result of any cause, progression to AP or BC, loss of major CyR, or loss of CHR.

### Safety Analysis

Safety analyses included all patients who received at least one dose of study medication. Patients were analyzed according to the dose received at the start of the treatment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

### Statistical Analysis

Efficacy analyses were performed on the intent-to-treat (ITT) regardless of dose escalation. When response rates at any particular time point were evaluated, patients with missing data at that assessment were treated like nonresponders in the ITT analysis (exceptions described in the *End Points* section).

A two-sided Fisher's exact test at the 5% alpha level was used for comparison of MMR rates. An exploratory Cochran-Mantel-Haenszel test stratified by baseline Sokal score was performed to account for the effect of Sokal score on MMR.

Time to response, duration of response, and long-term end points were analyzed by using the Kaplan-Meier method, and treatment differences were evaluated by log-rank test. Patients who discontinued study drug were observed for survival every 3 months.

### Ethics and Study Management

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was reviewed by the ethics committee or review board at each participating institution. Patients were required to give written informed consent. This trial was registered at <http://www.clinicaltrials.gov> as NCT00124748.

**Table 1.** Baseline Demographic and Clinical Characteristics

Characteristic	Patients by Imatinib Dose					
	400 mg (n = 157)		800 mg (n = 319)		All (N = 476)	
	No.	%	No.	%	No.	%
Age, years						
Median	45		48		47	
Range	18-75		18-75		18-75	
Male sex	84	53.5	183	57.4	267	56.1
ECOG performance status						
0	124	79.0	244	76.5	368	77.3
1	28	17.8	64	20.1	92	19.3
2	2	1.3	5	1.6	7	1.5
Ethnicity						
Asian	22	14.0	42	13.2	64	13.4
Black	12	7.6	17	5.3	29	6.1
White	109	69.4	241	75.5	350	73.5
Other	14	8.9	19	6.0	33	6.9
Time since diagnosis, days						
Median	28		28		28	
Range	-6 to 193*		1 to 217		-6 to 217*	
Sokal risk group						
Low	62	39.5	135	42.3	197	41.4
Intermediate	53	33.8	111	34.8	164	34.5
High	42	26.8	73	22.9	115	24.2
Prior treatment						
Hydroxyurea	109	69.4	227	71.2	336	70.6
Anagrelide	1	0.6	5	1.6	6	1.3
Imatinib	3	1.9	13	4.1	16	3.4

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

\*One patient was enrolled on the basis of first results received, and final cytogenetic confirmation was 6 days after random assignment.

## RESULTS

### Patients and Treatment

Between June 2005 and December 2006, 476 patients were randomly assigned to imatinib 800 mg/d (n = 319) or 400 mg/d (n = 157) at 103 sites in 19 countries. This analysis is based on data collected until December 31, 2007, after all patients had reached at least 1 year of study treatment or had discontinued treatment. The median follow-up was 17 months for both arms. There were no clinically significant differences in baseline characteristics between arms (Table 1).

Median duration of imatinib exposure was comparable between arms: 16.8 months in the 400-mg/d arm (range, 1.6 to 28.1 months) and 16.3 months in the 800-mg/d arm (range, 0.3 to 29.9 months). At data cutoff, 388 (81.5%) of 476 randomly assigned patients were still on study treatment (Table 2). Treatment discontinuation occurred in 15.9% of patients randomly assigned to imatinib 400 mg/d and in 19.7% of patients randomly assigned to imatinib 800 mg/d. The most frequent reasons for discontinuation were adverse events in the high-dose arm and unsatisfactory therapeutic effect in the 400-mg/d arm.

### Efficacy

**Molecular response.** There was no statistically significant difference in the rate of MMR at 12 months between the two arms in the ITT analysis (40.1% v 46.4% for the 400-mg/d and 800-mg/d arms, respectively;  $P = .2035$ ) or among evaluable patients (ie, those with PCR data available at each time point;  $P = .1386$ ; Table 3). However, MMR was achieved more rapidly among patients randomly

**Table 2.** Patient Disposition and Discontinuation Reasons

Variable	Patients by Imatinib Dose			
	400 mg (n = 157)		800 mg (n = 319)	
	No.	%	No.	%
Treatment disposition				
Continued initial treatment	132	84.1	256	80.3
Discontinued initial treatment	25	15.9	63	19.7
Reason for discontinuation				
Adverse events	6	3.8	30	9.4
Abnormal laboratory value(s)	1	0.6	2	0.6
Unsatisfactory therapeutic effect	10	6.4	20	6.3
Patient withdrew consent	2	1.3	4	1.3
Protocol violation	3	1.9	1	0.3
Administrative problems	2	1.3	2	0.6
No longer required study drug	1	0.6	1	0.3
Lost to follow-up	0		2	0.6
Death	0		1	0.3
Most frequent adverse events leading to discontinuation*				
Rash	1	0.6	5	1.6
Neutropenia	1	0.6	4	1.3
Nausea	1	0.6	3	0.9
Dyspnea	0		3	0.9
Thrombocytopenia	2	1.3	1	0.3

NOTE. Disposition in the intent-to-treat population as of December 31, 2007 (ie, data cutoff).

\*Safety population.

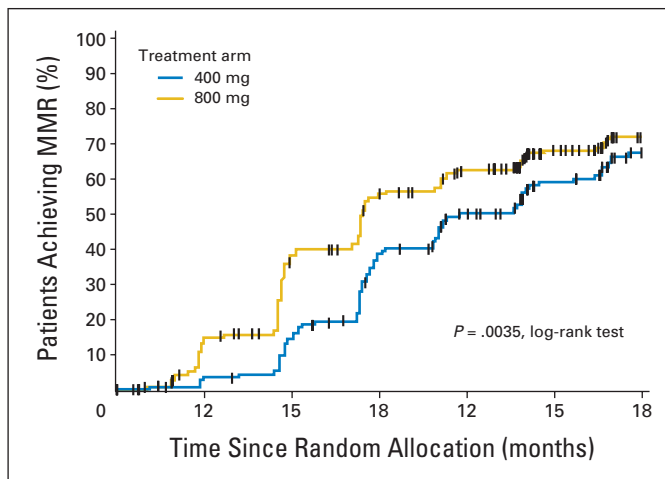
**Table 3.** Response Rates Over Time and by Sokal Risk

Variable	Patients by Imatinib Dose						P
	400 mg/d			800 mg/d			
	No. With Response	No. Evaluated	% of Evaluated With Response	No. With Response	No. Evaluated	% of Evaluated With Response	
MMR at time point, months							
3	5	157	3.2	39	319	12.2	.001
6	27	157	17.2	107	319	33.5	.0002
9	56	157	35.7	144	319	45.1	.06
12*	63	157	40.1	148	319	46.4	.2035
MMR in evaluable patients at time point, months							
3	5	137	3.6	39	283	13.8	.001
6	27	135	20.0	107	276	38.8	.001
9	56	136	41.2	144	267	53.9	.0203
12	61	133	45.9	145	269	53.9	.1386
MMR at 12 months by Sokal risk group							
Low	26	62	41.9	68	135	50.4	.286
Intermediate	24	53	45.3	48	111	43.2	.867
High	11	42	26.2	29	73	39.7	.160
Cumulative incidence of CCyR by time point, months							
6	70	157	44.6	181	319	56.7	.015
12	103	157	65.6	223	319	69.9	.347
CCyR by 12 months by Sokal risk group							
Low	43	62	69.4	105	135	77.8	.2177
Intermediate	34	53	64.2	72	111	64.9	1.0
High	26	42	61.9	46	73	63.0	1.0

NOTE. Data are based on intent-to-treat populations unless otherwise specified. Abbreviations: MMR, major molecular response; CCyR, complete cytogenetic response. \*Primary end point, allowing for imputation.

assigned to imatinib 800 mg/d compared with those randomly assigned to imatinib 400 mg/d ( $P = .0035$  by log-rank test; Fig 2). This corresponded to significantly higher MMR rates for patients treated in the high-dose arm in earlier time periods (Table 3).

There was a correlation between MMR rate and average dose-intensity (ie, actual dose divided by time on treatment in mg/d) in the 800-mg/d arm. At 12 months, MMR was observed in 83 (62%) of 134 patients with an average dose intensity of 600 to 799 mg/d, and it was observed in 26 (38%) of 69 patients with an average dose intensity of 400 to 599 mg/d (Fig 3).

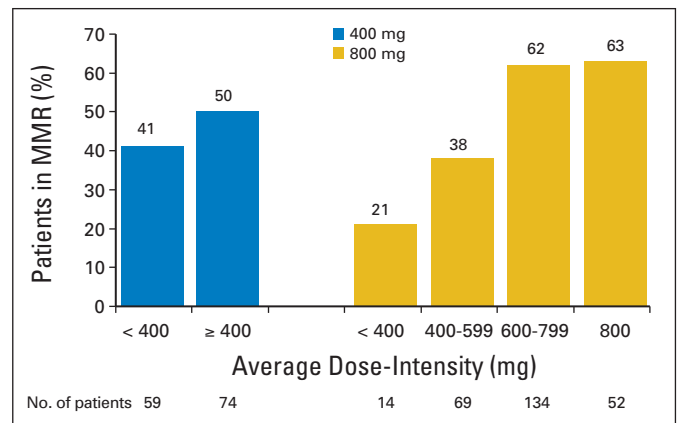


**Fig 2.** Time to first major molecular response (MMR) by treatment arm (intent-to-treat analysis).

The rate of MMR at 12 months did not differ significantly between arms according to Sokal risk group (Table 3). However, when best molecular response by 12 months (ie, at any time during the first 12 months since random assignment) was evaluated in high-risk patients, 31.0% on imatinib 400 mg/d achieved an MMR compared with 50.7% on imatinib 800 mg/d ( $P = .05$ ).

**Cytogenetic Response**

By 6 months, 70 (44.6%) of 157 patients randomly assigned to the standard dose of imatinib achieved CCyR compared with 181 (56.7%) of 319 patients randomly assigned to high-dose imatinib



**Fig 3.** Major molecular response (MMR) at 12 months by average dose intensity (evaluable patients).

( $P = .01$ ; Table 3). By 12 months, CCyR rates were comparable between arms (65.6% and 69.9% in the 400-mg/d and 800-mg/d arms, respectively). There was no significant difference in CCyR rates within Sokal risk category (Table 3).

### Long-Term Outcomes

The estimated PFS rates at 18 months were 95.0% (95% CI, 90.2% to 99.8%) for the 400-mg/d arm and 97.4% (95% CI, 95.3% to 99.6%) for the 800-mg/d arm ( $P = .63$ ). Among patients with high Sokal risk, PFS rates were 88.1% versus 95.9% for the 400-mg/d arm and the 800-mg/d arm, respectively. Progression to AP/BC on treatment occurred in five (3.2%) of 157 patients in the 400-mg/d arm and in six (1.9%) of 319 patients in the 800-mg/d arm. The estimated OS rate at 18 months was 98.7% (98.7% v 98.2% for 400 mg v 800 mg, respectively;  $P = .56$ ).

### Bone Marrow Transplantation

Seven patients (1.5%) underwent bone marrow transplantation (BMT) after study discontinuation; one was in the 400-mg/d arm, and six were in the 800-mg/d arm. At the time of BMT, one patient was in MMR. The other six patients who received BMT had no or minimal CyR and no molecular response at the time of transplantation. Two patients underwent BMT after progression to BC ( $n = 1$  in the 400-mg/d arm;  $n = 1$  in the 800-mg/d arm).

### Safety and Tolerability

**Dose-intensity.** The average daily doses of imatinib were 388.4 mg in the 400-mg/d arm (range, 177 to 663 mg) and 662.0 mg in the 800-mg/d arm (range, 223 to 800 mg). This represents an average relative dose intensity of 97% and 83%, respectively. More than 50% of patients in the 800-mg/d arm received an average daily imatinib dose of at least 750 mg/d, 25% tolerated an average dose of at least 793 mg/d, and 75% tolerated 546 mg/d or more. Among the 433 patients still on treatment at 12 months, 61% of patients in the 800-mg/d arm were being treated with their assigned dose, and 78% of patients in this arm were receiving imatinib at least 600 mg/d.

Although dose increases were not permitted in the 800-mg/d arm, 11 patients (7.0%) in the 400-mg/d arm increased their doses to between 600 and 800 mg/d. Dose reductions were required in 28 patients (17.8%) in the 400-mg/d arm and in 194 patients (61.4%) in the 800-mg/d arm. In the 400-mg/d arm, 81 patients (52%) had at least 1 day of zero dose until data cutoff (with 7, 19, and 43 days representing the 25th, 50th, and 75th percentiles). Among patients in the 800-mg/d arm, 233 (73%) reported at least 1 day of zero dose (and 11, 21, and 38 days represented the 25th, 50th, and 75th percentiles). Half of patients (50.0%) in the 800-mg/d arm had at least one dose reduction to less than 600 mg/d. Dose interruptions lasting more than 5 days were experienced by 59 patients (37.6%) in the 400-mg/d arm and by 211 patients (66.8%) in the 800-mg/d arm. The most common reason for dose reduction was adverse event/laboratory abnormality, cited in 52 patients (33.1%) in the 400-mg/d arm and in 230 patients (72.8%) in the 800-mg/d arm. The median durations of imatinib dose reduction through month 12 were 95 days (range, 3 to 342 days) for the standard dose and 115 days (range, 1 to 335 days) for the high dose. The median durations of days without drug in the same time period were 15 days (range, 1 to 95 days) for the standard dose and 20 days (range, 1 to 160 days) for the high dose of imatinib.

### Adverse Events

The majority of adverse events judged by the investigator to be related to study drug in both arms were mild or moderate in intensity and resolved spontaneously or with dose interruptions or reductions if needed. Overall, 147 patients (93.6%) in the 400-mg/d arm and 310 (98.1%) in the 800-mg/d arm reported adverse events (all grades), and 52 (33.1%) and 201 (63.6%) reported grades 3 to 4 adverse events, respectively. Rates of all-grade and grades 3 to 4 (Table 4) hematologic adverse events were higher in the 800-mg/d arm. The incidence of biochemical abnormalities did not differ according to dose. More patients in the 800-mg/d arm discontinued imatinib because of adverse events (3.8% v 9.4%; Table 2).

### Death

Eight patients (1.7%) died; one died on study about 2 months after last study drug was taken, and seven died after discontinuation of

**Table 4.** Most Frequently Reported Grades 3 to 4 Study Drug-Related Adverse Events

Adverse Event	Patients by Imatinib Dose			
	400 mg (n = 157)		800 mg (n = 319)	
	No.	%	No.	%
<b>Nonhematologic*</b>				
Nausea	0		4	1.3
Periorbital edema	0		3	0.9
Diarrhea	0		8	2.5
Peripheral edema	0		2	0.6
Rash	4	2.5	18	5.7
Muscle spasms	1	0.6	3	0.9
Fatigue	3	1.9	5	1.6
Vomiting	1	0.6	3	0.9
Arthralgia	1	0.6	6	1.9
Myalgia	0		11	3.5
Face edema	0		2	0.6
Pain in extremity	0		7	2.2
Headache	0		5	1.6
Eyelid edema	0		2	0.6
Dyspepsia	0		0	
Dizziness	0		3	0.9
<b>Hematologic†</b>				
Leukopenia	12	7.6	45	14.2
Neutropenia	29	18.5	90	28.5
Thrombocytopenia	16	10.2	57	18.0
Anemia	6	3.8	22	7.0
<b>Laboratory abnormalities‡</b>				
Hypophosphatemia	23	14.6	38	12.0
Hypocalcemia	6	3.8	4	1.3
Transaminase elevation	7	4.5	9	2.8
Alkaline phosphatase	0		1	0.3
ALT	7	4.5	8	2.5
AST	5	3.2	5	1.6
Albumin	0		1	0.3
Creatinine	0		1	0.3
Total bilirubin	0		0	
Hypercalcemia	1	0.6	0	

NOTE. Most frequent adverse events occurred in at least 10% of patients from either treatment group.

\*Most frequently reported nonhematologic adverse events determined by the investigator to be study drug related.

†Newly occurring or worsening abnormalities on the basis of laboratory values.



study treatment. Of those who died, two were assigned to the 400-mg/d arm, and six were assigned to the 800-mg/d arm. Both patients on standard-dose imatinib who died discontinued treatment because of unsatisfactory therapeutic effect (n = 1 in CHR with no CyR at time of discontinuation; n = 1 with no CHR or CyR) and died during follow-up (n = 1 because of fungal infection 3.5 months after stopping imatinib; n = 1 because of CML 2 months after stopping study treatment). Of the six patients who died in the 800-mg/d arm, one patient died of pulmonary tuberculosis while on study but did not receive study drug for 2 months before death, and five died after discontinuation of treatment (n = 3 as a result of CML; n = 2 as a result of complications subsequent to bone marrow transplantation).

## DISCUSSION

Data from the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study suggest that imatinib 400 mg/d should remain the initial therapy for the majority of patients with CML. High-dose (ie, 800 mg/d) imatinib also was well tolerated in most patients and was associated with a more rapid response than the standard dose (ie, 400 mg/d) of imatinib, but MMR rates at 12 months—the primary end point of the study—were comparable between arms. Grades 3 to 4 adverse events were uncommon in this study, and there were no new adverse events associated with imatinib that had not been identified previously. Adverse events, although more frequent with imatinib 800 mg/d, were manageable in most cases with dose interruptions or dose reductions.

The majority of patients achieved a CyR by 6 months. The CCyR and MMR rates at 12 months for patients treated with 400 mg/d on the TOPS study were comparable with those seen on the IRIS trial in the same time period.<sup>4,18</sup> Rates of discontinuation overall were comparable, but they did appear to be higher on the TOPS study (even for the standard-dose cohort) than on the IRIS trial for adverse events and unsatisfactory therapeutic effect; this is likely because of the availability of the second-generation tyrosine kinase inhibitors nilotinib and dasatinib. The estimated rates of PFS and OS at 18 months were greater than 95% for patients in both treatment arms on the TOPS study.

Although half of the patients in the 800-mg/d arm required dose reduction to less than 600 mg/d at some point on study, the average daily dose of imatinib for patients in the 800-mg/d arm was 662 mg/d. More than half of the patients in the 800-mg/d arm received an average dose of at least 750 mg/d, and 75% tolerated approximately 600 mg/d or more. These data suggest that the increased adverse events associated with imatinib 800 mg/d were manageable by following protocol dosing guidelines. Although the number of imatinib tablets dispensed and returned was recorded, and although imatinib blood levels were higher among patients randomly assigned to the 800-mg/d arm,<sup>19</sup> the possibility that some patients may have had dose reductions or interruptions that were not reported cannot be excluded.

In the 800-mg/d arm, patients who received a median imatinib dose of at least 600 mg/d had the greatest probability of achieving an MMR, and patients who received less than 400 mg/d had the worst outcome (Fig 3). Interestingly, patients in the 800-mg/d arm who received an average dose intensity of less than 400 mg/d fared far worse than those randomly assigned to 400 mg/d who had the same dose intensity, as MMR rates were 21% and 41% at 12 months, respectively. This may be because patients randomly assigned to imatinib 800 mg/d who experienced dose reductions to less than 400 mg/d had more days

off drug than patients randomly assigned to 400 mg/d with similar dose reductions. These data suggest that patients who can tolerate high-dose imatinib achieve superior cytogenetic and molecular responses compared with those who need dose modification and suggest that the number of days off medication may adversely impact outcomes. Other confounding factors that may contribute to a patient's ability to maintain dose intensity (eg, high plasma  $\alpha$ -1-acid glycoprotein levels or other factors associated with increased adverse events<sup>20-23</sup>) were not investigated in this study.

In this study, imatinib 800 mg/day induced earlier CCyR and MMR in patients with newly diagnosed CML-CP. Differences in MMR rates at 3 and 6 months, time to first MMR, and CCyR rates at 6 months between the treatment arms were statistically significant ( $P = .001, .0002, .0035, \text{ and } .013$ , respectively). A significantly greater proportion of patients in the 800-mg/d arm achieved an early (within 6 months) CCyR. By 12 months, MMR rates were comparable between arms. The reasons for this are unknown. It is possible that, over time, the inhibitory effect of imatinib reaches a plateau that is attained earlier with high-dose imatinib and later with the standard dose.

Higher-risk patients may be potential candidates for initial therapy with high-dose imatinib, as more patients with high Sokal risk in the 800-mg/d arm achieved an MMR compared with the 400-mg/d arm when best molecular response by 12 months was evaluated. In a recent study conducted by the European LeukemiaNet, rates of MMR and CCyR were comparable between patients with newly diagnosed CML-CP who had high Sokal risk and who were treated with 800 mg/d versus 400 mg/d imatinib.<sup>24</sup> However, as in the TOPS study, CCyR rates appeared to be related to the actual dose received (ie, 91% for 700 to 800 mg/d, 73% for 400 to 699 mg/d, and 20% for < 400 mg/d). Dose-intensity also correlated with response in other trials of higher-dose imatinib in patients with newly diagnosed CML-CP.<sup>11,12</sup>

The safety and efficacy of imatinib 400 mg/d for patients with newly diagnosed CML-CP was confirmed in the TOPS study. Response and safety findings for patients treated with standard-dose imatinib were similar to those seen in the IRIS trial. Longer follow-up is required to determine whether the earlier responses induced by high-dose imatinib will translate into improved long-term outcomes.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Employment or Leadership Position:** Marc Rudoltz, Novartis (C); Richard Yu, Novartis (C); Tillmann Krahnke, Novartis (C) **Consultant or Advisory Role:** Michele Baccarani, Novartis (C), Bristol-Myers Squibb (C); François Guilhot, Novartis (C), Bristol-Myers Squibb (C); Brian J. Druker, Novartis (U); Susan Branford, Novartis (C), Bristol-Myers Squibb (C); Dong-Wook Kim, Novartis (C), Bristol-Myers Squibb (C); Fabrizio Pane, Novartis (C), Bristol-Myers Squibb (C); Beatriz Moiraghi, Bristol-Myers Squibb (C); Jerald P. Radich, Novartis (C); Timothy P. Hughes, Bristol-Myers Squibb (C), Novartis (C) **Stock Ownership:** Brian J. Druker, MolecularMD; Marc Rudoltz, Novartis; Richard Yu, Novartis; Tillmann Krahnke, Novartis

**Honoraria:** Michele Baccarani, Novartis, Bristol-Myers Squibb; François Guilhot, Novartis, Bristol-Myers Squibb; Susan Branford, Novartis, Bristol-Myers Squibb; Dong-Wook Kim, Novartis, Wyeth, Bristol-Myers Squibb; Ricardo Pasquini, Novartis, Bristol-Myers Squibb; Stuart L. Goldberg, Novartis; Matt Kalaycio, Novartis; Jerald P. Radich, Novartis; Timothy P. Hughes, Novartis, Bristol-Myers Squibb **Research Funding:** Jorge E. Cortes, Novartis, Bristol-Myers Squibb, Wyeth; Michele Baccarani, Novartis; Brian J. Druker, Novartis, Bristol-Myers Squibb; Susan Branford, Novartis, Bristol-Myers Squibb; Dong-Wook Kim, Novartis, Wyeth, Bristol-Myers Squibb; Fabrizio Pane, Novartis; Stuart L. Goldberg, Novartis; Matt Kalaycio, Novartis; Hagop M. Kantarjian, Genzyme, Novartis, Bristol-Myers Squibb; Jerald P. Radich, Novartis; Timothy P. Hughes, Novartis, Bristol-Myers Squibb **Expert Testimony:** None **Other Remuneration:** Brian J. Druker, Dana-Farber Cancer Institute, Oregon Health Sciences University (Patent No. 843)

## AUTHOR CONTRIBUTIONS

**Conception and design:** Jorge E. Cortes, Michele Baccarani, François Guilhot, Brian J. Druker, Marc Rudoltz, Richard Yu, Hagop M. Kantarjian, Jerald P. Radich, Timothy P. Hughes

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**Administrative support:** Richard Yu

**Provision of study materials or patients:** Jorge E. Cortes, Michele Baccarani, François Guilhot, Brian J. Druker, Dong-Wook Kim, Ricardo Pasquini, Stuart L. Goldberg, Matt Kalaycio, Beatriz Moiraghi, Jacob M. Rowe, Elena Tothova, Carmino De Souza, Hagop M. Kantarjian, Timothy P. Hughes

**Collection and assembly of data:** Jorge E. Cortes, Michele Baccarani, Susan Branford, Dong-Wook Kim, Fabrizio Pane, Stuart L. Goldberg, Elena Tothova, Carmino De Souza, Marc Rudoltz, Jerald P. Radich, Timothy P. Hughes

**Data analysis and interpretation:** Brian J. Druker, Susan Branford, Dong-Wook Kim, Fabrizio Pane, Marc Rudoltz, Tillmann Krahnke, Jerald P. Radich, Timothy P. Hughes

**Manuscript writing:** Brian J. Druker, Susan Branford, Stuart L. Goldberg, Jacob M. Rowe, Marc Rudoltz, Tillmann Krahnke, Jerald P. Radich, Timothy P. Hughes

**Final approval of manuscript:** Jorge E. Cortes, Michele Baccarani, François Guilhot, Brian J. Druker, Susan Branford, Dong-Wook Kim, Fabrizio Pane, Ricardo Pasquini, Stuart L. Goldberg, Matt Kalaycio, Jacob M. Rowe, Elena Tothova, Carmino De Souza, Marc Rudoltz, Jerald P. Radich, Timothy P. Hughes

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