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ORIGINAL REPORT

Deep Molecular Response Is Reached by the Majority of Patients Treated With Imatinib, Predicts Survival, and Is Achieved More Quickly by Optimized High-Dose Imatinib: Results From the Randomized CML-Study IV

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ABSTRACT

Purpose
Deep molecular response ($MR^{4.5}$) defines a subgroup of patients with chronic myeloid leukemia (CML) who may stay in unmaintained remission after treatment discontinuation. It is unclear how many patients achieve $MR^{4.5}$ under different treatment modalities and whether $MR^{4.5}$ predicts survival.

Patients and Methods
Patients from the randomized CML-Study IV were analyzed for confirmed $MR^{4.5}$ which was defined as ≥ 4.5 log reduction of BCR-ABL on the international scale (IS) and determined by reverse transcriptase polymerase chain reaction in two consecutive analyses. Landmark analyses were performed to assess the impact of $MR^{4.5}$ on survival.

Results
Of 1,551 randomly assigned patients, 1,524 were assessable. After a median observation time of 67.5 months, 5-year overall survival (OS) was 90%, 5-year progression-free-survival was 87.5%, and 8-year OS was 86%. The cumulative incidence of $MR^{4.5}$ after 9 years was 70% (median, 4.9 years); confirmed $MR^{4.5}$ was 54%. $MR^{4.5}$ was reached more quickly with optimized high-dose imatinib than with imatinib 400 mg/day ($P = .016$).

Independent of treatment approach, confirmed $MR^{4.5}$ at 4 years predicted significantly higher survival probabilities than 0.1% to 1% IS, which corresponds to complete cytogenetic remission (8-year OS, 92% *v* 83%; $P = .047$). High-dose imatinib and early major molecular remission predicted $MR^{4.5}$. No patient with confirmed $MR^{4.5}$ has experienced progression.

Conclusion
$MR^{4.5}$ is a new molecular predictor of long-term outcome, is reached by a majority of patients treated with imatinib, and is achieved more quickly with optimized high-dose imatinib, which may provide an improved therapeutic basis for treatment discontinuation in CML.

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INTRODUCTION

In chronic myeloid leukemia (CML), the depth of response is considered an indicator for residual tumor mass and, thus, for survival. Patients who have achieved complete cytogenetic remission (CCR) have a life expectancy similar to that of the general population.[1] Patients with deeper responses, such as major molecular remission (MMR), MR^4, and $MR^{4.5}$ have, thus far, not been shown to survive longer than those with CCR. Patients in deep remissions are assumed to have more stable remissions with lower probabilities of progression, allowing discontinuation of therapy.[2,3] Little is known on the proportion of patients who can achieve MR^4 or $MR^{4.5}$. The IRIS study provides information on deep molecular response in only a subgroup of patients[4] because standardized molecular monitoring was not generally available in 2000 when the study started. Branford et al[5] reported in a cohort of 415 patients a stable undetectable $MR^{4.5}$ rate of 36.5% at 8 years.

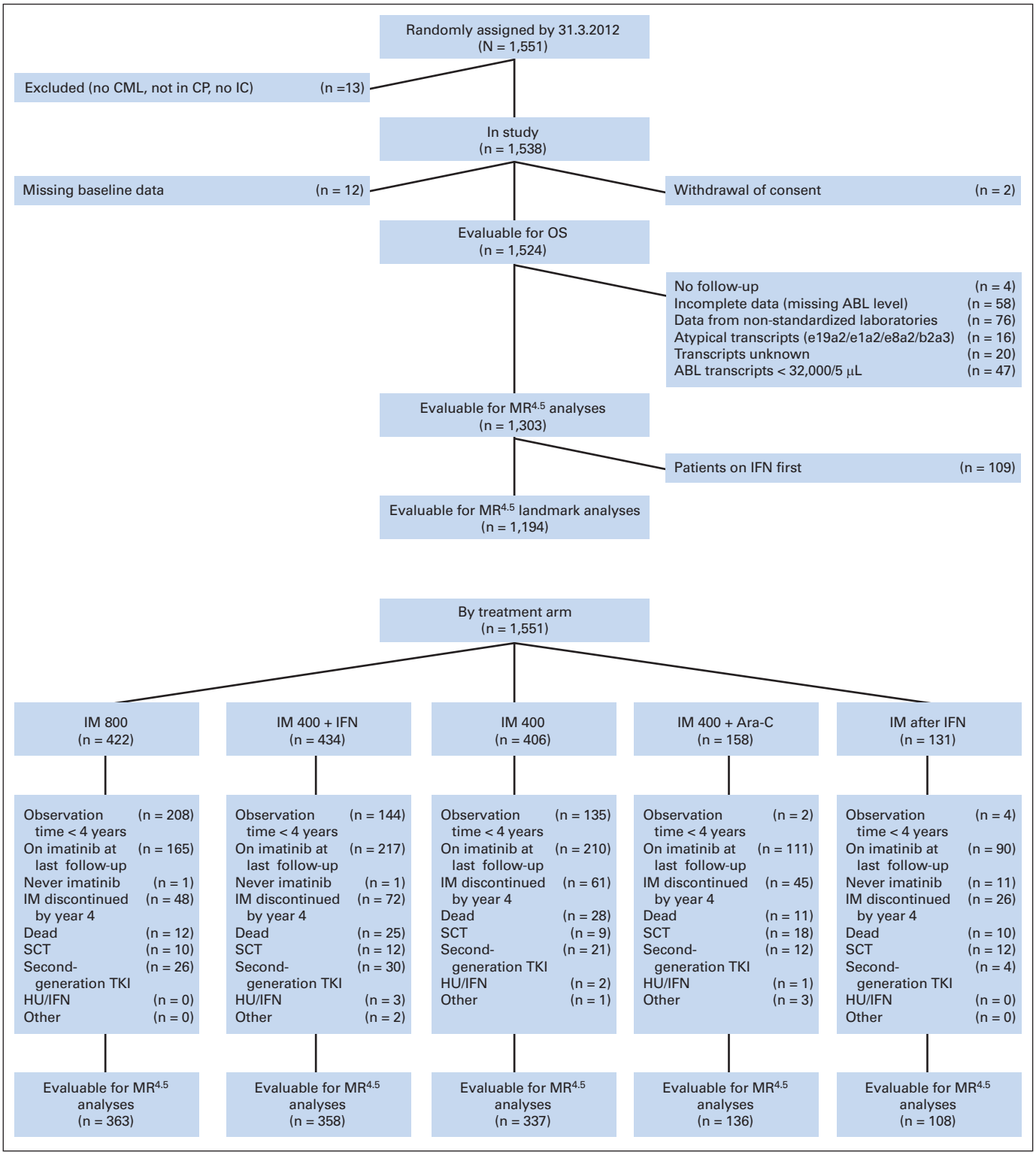

Fig 1. Flow diagram of randomly assigned and assessable patients. CML, chronic myeloid leukemia; CP, chronic phase; HU, hydroxyurea; IC, informed consent; IFN, interferon alfa; IM, imatinib; OS, overall survival; SCT, stem-cell transplantation; second gen. TKI, second-generation tyrosine kinase inhibitor.

In CML-Study IV, molecular monitoring was performed as an integral part of the study from the beginning. We have shown previously that optimized high-dose imatinib induced faster and deeper cytogenetic and molecular responses (CCR, MMR, MR^4) than did standard imatinib at 400 mg/day.[6]

Because $MR^{4.5}$ defines a subgroup of patients who may stay in unmaintained remission after discontinuation of treatment, it was our

goal to determine the proportion of patients achieving $MR^{4.5}$, and to analyze whether $MR^{4.5}$ is reached faster with optimized high-dose imatinib and whether the achievement of $MR^{4.5}$ results in better survival than the achievement of less deep remissions.

PATIENTS AND METHODS

Study Design and Goals

CML-Study IV is a five-arm randomized study comparing imatinib 400 mg/day versus imatinib 400 mg/day in combination with interferon alfa (IFN) versus imatinib 400 mg/day in combination with low-dose cytarabine versus imatinib 400 mg/day after IFN failure versus imatinib 800 mg/day. Recruitment was from July 2002 through March 2012. Only low- and intermediate-risk patients were assigned to receive primary IFN and, during a pilot-phase of 3 years, only high-risk patients to imatinib 800 mg/day. In 2005, recruitment to imatinib plus cytarabine and imatinib after IFN failure was terminated, and imatinib 800 mg/day started as a full study arm. The first primary goal of CML-Study IV was to determine the impact of MMR on survival at 12 months.[6] Other primary objectives were remission rates and survival probabilities. Secondary objectives included identification of prognostic factors,[7,8] long-term toxicity, impact of remission-rates on survival, and outcome of patients undergoing transplantation after imatinib pretreatment.[9] A comparative survival analysis is planned 5 years after completion of recruitment.

Treatment

Initial treatment in all study arms except the arm imatinib after IFN failure was imatinib 400 mg once daily. If no complete hematologic remission (CHR) was reached after 2 months or no partial cytogenetic remission after 6 months, a dose increase to 600 mg/day or 800 mg/day was permitted.

The full 800-mg/day dose was administered after a 6-week run-in period with imatinib 400 mg/day to avoid excessive cytopenias. The dose could be reduced according to tolerability. Higher-grade adverse events (AEs), mainly grade 3 and 4, were to be avoided to not compromise patients' compliance and to avoid clinical risks. If imatinib treatment failed, either stem-cell transplantation (SCT) or risk-adapted drug treatment (hydroxyurea [HU], cytarabine, intensive chemotherapy) was recommended depending on type of mutation and degree of proliferation or progression.[10] After approval of second-generation tyrosine kinase inhibitors (TKI), either nilotinib or dasatinib was recommended.

IFN was added 6 weeks after the start of imatinib at an initial dose of 1.5 million U and increased up to 3 million U three times per week according to

Table 1. Characteristics of Patients and Treatments (n = 1,538)

Characteristic	Imatinib 400 mg/day (n = 401) No.	%	Imatinib + IFN (n = 430) No.	%	Imatinib + Cytarabine (n = 158) No.	%	Imatinib after IFN(n = 129) No.	%	Imatinib 800 mg/day (n = 420) No.	%
Age, years										
Median	53		53		51		53		51	
Range	16-88		16-83		18-79		18-87		18-85	
Sex										
Female		39		41		37		37		41
Hemoglobin, g/dL										
Median	12.4		12.2		12.5		12.9		12.2	
Range	4.9-17.5		6.2-17.7		6.7-15.9		8.1-17.6		4.7-19.1	
WBC $\times 10^9$/L										
Median	76.6		89.4		57.8		55.9		80.1	
Range	5.7-581.6		2.8-630.3		2.9-529.0		3.2-456.0		2.6-586.5	
Platelets $\times 10^9$/L										
Median	382		343		402.5		390		387	
Range	58-2,419		49-3,020		34-2,799		44-2,205		39-2,716	
EUTOS score										
Low		88		90		88		92		85
High		12		10		12		8		15
Median time from diagnosis to random assignment, days	17		16		19		16		15	
Median observation time, months	66		68		92		92		50	
Dose per actual treatment day, mg										
Months 0-3	400		400		400		400		552	
Months 3-6	400		400		400		400		661	
Months 6-9	400		400		400		400		600	
Months 9-12	400		400		400		400		524	
Months 12-18	400		400		400		400		446	
Months 18-24	400		400		400		400		429	
Months 24-30	400		400		400		400		427	
Months 30-36	400		400		400		400		400	
Months 36-42	400		400		400		400		400	
Months 42-48	400		400		400		400		400	
Median	400		400		400		400		505	
Range	179-743		96-800		194-665		251-612		277-800	

Abbreviations: EUTOS, European Treatment and Outcome Study; IFN, interferon alfa.

tolerability. The IFN dose was adapted to avoid WBC less than 2,000/μL and platelets less than 50,000/μL. The IFN dose was halved at WBC less than 1,000/μL or platelets less than 100,000/μL and was interrupted at WBC less than 500/μL or platelets less than 50,000/μL at a constant imatinib dose.

Subcutaneous cytarabine was added 6 weeks after the start of imatinib at the initial dose of 10 mg/day on 2 $\times$ 5 days/month. Depending on tolerability, the dose could be escalated to 20 mg/m^2/day 2 $\times$ 5 days/month cytarabine was discontinued, if no CCR was achieved after 18 months.

In the imatinib after IFN failure arm, IFN (IFNα2a or IFNα2b) was administered after initial cytoreduction with HU (40 mg/kg/day) initially at 3 million U/day subctaneously and slowly escalated to 5 million U/m^2/day (total of 9 million U/day). Dosages of IFN and HU should aim at WBC of 2,000 to 4,000/μL.

IFN failure was defined as no CHR after 6 months or not at least partial cytogenetic remission ($\leq$ 35% Ph positivity) after 21 months, loss of CHR or CCR, or higher-grade AE. After IFN failure, patients were switched to imatinib 400 mg/day.

Definitions and End Points

Definitions followed the recommendations published by the European LeukemiaNet in 2006 and 2009.[11,12] Risk assignment was made by using the European Treatment and Outcome Study (EUTOS) score criteria.[13] The starting date for all time-to-event analyses was the date of diagnosis. Overall survival (OS) was defined as the time between diagnosis and death resulting from any cause whether during TKI treatment or not. Progression-free-survival (PFS) considered the additional events accelerated phase (AP) and blast crisis (BC). All living patients were censored at the time of their last visit. When estimating the cumulative incidences of molecular or cytogenetic remissions, patients were censored when they received a second-generation TKI. No patient was removed from the study except at the patient's request (n = 4).

Cytogenetic and Molecular Analyses

Cytogenetic analyses were performed after short-term culture (24 hours, 48 hours, or both) with standard G-banding or fluorescence *R*-banding techniques. For follow-up analyses of CCR, at least 20 marrow-cell metaphases were evaluated. Molecular diagnostics for residual BCR-ABL transcripts followed the procedures and definitions of Hughes et al[14] and Cross et al,[15] and were performed in two standardized and accredited laboratories with defined conversion factors for equivalence of tests (Mannheim and MLL Munich).[16] The analysis of molecular end points was restricted to patients expressing b2a2 and/or b3a2 transcripts. Confirmed MR^4 and MR$^{4.5}$ were defined as a reduction of residual BCR-ABL transcripts of $\geq$ 4 and $\geq$ 4.5 logs compared to the standardized baseline in two consecutive analyses.[15,17] In case of a positive quantitative reverse-transcription polymerase chain reaction (qRT-PCR) for BCR-ABL transcripts, BCR-ABL (IS) $\leq$ 0.01% was designated MR^4 and BCR-ABL (IS) less than 0.0032% as MR$^{4.5}$. For a negative qRT-PCR and positive nested RT-PCR, the lowest positive plasmid-standard/ABL ratio had to be $\leq$ 0.01% or $\leq$ 0.0032%, respectively. For a negative qRT-PCR and a negative nested PCR, the number of ABL transcripts used for nested PCR had to be $\geq$ 10,000 for MR^4 and $\geq$ 32,000 for MR$^{4.5}$.

Statistical Analysis

Cumulative incidences were calculated under consideration of competing risks[18] defined by AP, BC, and death. Comparisons between cumulative incidences were performed by Gray test.[19] Landmark analyses[20] were performed to evaluate the prognostic impact of different remissions on survival. Influence of response status (less than CCR *v* CCR *v* MR$^{4.5}$) was investigated using time-dependent Cox regression. Significance was judged by the likelihood ratio test. Conventional Cox regression with censoring of competing risk(s) was used for analyzing cause-specific hazards.[21] Because of the exploratory character of the landmark analyses, all *P* values have to be considered as descriptive. Analyses were according to intention to treat; only AEs were analyzed as treated to avoid bias by other treatments. Level of significance was .05. All calculations were performed with SAS software (SAS Institute, Cary, NC).

Ethics

The protocol followed the Declaration of Helsinki and was approved by the ethics committees of the Medizinische Fakultät Mannheim and of participating centers. Written informed consent was obtained from all patients before they entered the study.

RESULTS

Patients

Of 1,551 randomly assigned patients with newly diagnosed chronic phase (CP) CML, 1,538 were assessable at diagnosis and 1,524 for follow-up (Consort flow diagram, Fig 1); 1,409 were randomly assigned for primary imatinib and 129 for primary IFN. Two patients withdrew consent after random assignment. Data entry was closed on May 24, 2012.

Patient characteristics are shown in Table 1. All variables were distributed evenly between treatment groups without significant differences. Median age was 52 years and 40% were female. Median observation time (overall) was 67.5 months (range, 0.1 to 123.8), 5-year OS was 90.0% (95% CI, 88.2 to 91.0%), 5-year PFS was 87.5%

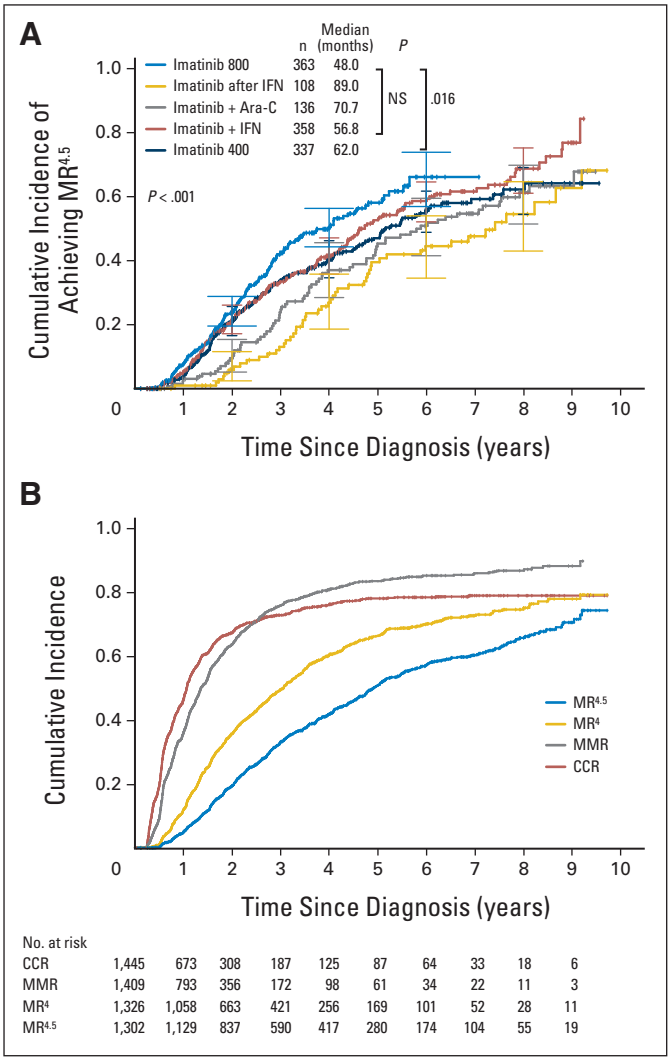

Fig 2. Cumulative incidence of (A) deep molecular response (MR$^{4.5}$) comparing all five treatment arms and of (B) complete cytogenetic remission (CCR), major molecular remission (MMR), MR^4, and MR$^{4.5}$ of all patients independent of therapy. Ara-C, cytarabine; IFN, interferon alfa; NS, not statistically significant.

(95% CI, 85.6 to 89.3%), and 8-year OS probability was 86% (95% CI, 84.0 to 88.5%). One hundred thirteen patients went on to undergo transplantation (73 in CP), 246 have received second-generation TKI, and 152 patients died (90 as a result of CML or unknown causes, 62 not directly CML related). These numbers are in part overlapping.

Molecular Response by Therapy

Figure 2A shows the cumulative incidences of $MR^{4.5}$ according to treatment arm. Patients with optimized high-dose imatinib achieved $MR^{4.5}$ more quickly than did patients with any other treatment, except imatinib plus IFN ($P = .016$). Median time to $MR^{4.5}$ was 48 months, 14 months shorter with imatinib 800 mg/day than with imatinib 400 mg/day (62 months). Similar results were observed with MR^4 (Table 2). Patients with imatinib after IFN failure achieved responses significantly later than did patients with imatinib 400 mg/day, imatinib 800 mg/day, and imatinib plus IFN.

Imatinib 800 mg/day was administered after a run-in period of 6 weeks at 400 mg/day and then reduced according to tolerability to avoid grade 3 or 4 AEs. The resulting median doses are shown in Table 1. In the 800-mg/day arm the median imatinib-dose showed a decline from 661 mg/day after 6 months to 400 mg/day after 3 years, with a median of 505 mg/day over the entire observation time. As a result of this strategy, the frequency of grade 3 or 4 AEs in the 800-mg/day arm was similar to that with imatinib 400 mg/day or imatinib + IFN (data not shown).

Molecular Response Independent of Therapy

Figure 2B shows the cumulative incidence of $MR^{4.5}$ independent of therapy, which reached 66% after 8 and 70% after 9 years compared with that of CCR, MMR, and MR.[4] The median time to $MR^{4.5}$over all treatments was 4.9 years. Stable molecular responses confirmed by at least one consecutive analysis at least 2 to 3 weeks apart were used for survival analyses. The level of confirmed $MR^{4.5}$ was 46% at 8 years.

Of 1,409 patients treated with primary imatinib, 1,194 were subjected to landmark analyses to evaluate the prognostic impact of different remission levels. To account for the median time to $MR^{4.5}$, we chose the time point 4 years. Independent of therapy, $MR^{4.5}$ at 4 years was associated with a significantly higher OS probability than 0.1% to 1% IS, which corresponds to CCR (8-year OS, 92% *v* 83%; $P = .047$; Fig 3A). The interim levels of 0.01% to 0.1% IS defined as MMR (8-year OS, 88%) and of 0.0032% to 0.01% IS defined as MR^4 (8-year OS, 90%) did not reach significance compared with $MR^{4.5}$ or with 0.1% to 1% IS. Exploratory analyses at 2, 3, and 5 years were inconclusive because there were too few patients with $MR^{4.5}$ or follow-up was too short.

No patient with $MR^{4.5}$ has experienced progression after a median observation time of 3 years. In comparison, after median observation times between 3.8 and 4.7 years, 13 patients have progressed after CCR (five are still alive as of this writing), nine after MMR (four still alive as of this writing) and one after MR^4 (who is still alive as of this writing; Table 3). The median age at progression was 60.9 years and has not been reached for death from other causes.

Early MMR predicted $MR^{4.5}$ as shown by the incidences of $MR^{4.5}$ according to level of molecular response at 3, 6, 12, and 18 months (Table 4). Of 1,194 assessable patients, 1,035 (87%) had at least one assessable molecular analysis in the period 3 to 18 months. Although patients missed tests, we think that this was at random and that the high absolute numbers of tests at each time point permit valid results. Patients with MMR at 3 and 6 months achieved $MR^{4.5}$ faster than did patients with MMR at 12 or 18 months or with higher response levels (0.1% to 1% IS, 1% to 10% IS or > 10% IS). The highest $MR^{4.5}$ level was reached with MMR at 3 months, with a cumulative $MR^{4.5}$ incidence of 83% at 5 years (Table 4). Figure 3B shows the incidences of $MR^{4.5}$ according to response levels at 6 months. MMR at 6 months resulted in a cumulative $MR^{4.5}$ incidence of 75% by 8 years.

Other potential prognostic factors for the achievement of $MR^{4.5}$ (e.g., risk-score at diagnosis, sex, age, therapy) were analyzed in a cause-specific hazards model. EUTOS low-risk (hazard ratio [HR] = 1.712; 95% CI, 1.253 to 2.339; $P < .001$), age younger than 65 years (HR = 1.278; 95% CI, 1.043 to 1.567; $P = .018$) and imatinib 800 mg/day (HR =

Table 2. Cumulative Incidences of Deep MR

	Year							
	2		4		6		8	
Cumulative Incidence	%	95% CI	%	95% CI	%	95% CI	%	95% CI
MR^4 by therapy								
IM 400 mg/day	35.4	30.1 to 40.7	60.0	54.0 to 65.5	69.4	63.2 to 74.7	77.5	69.1 to 83.9
IM + IFN	37.3	32.1 to 42.5	59.9	54.0 to 65.2	72.4	66.6 to 77.5	78.1	71.9 to 83.2
IM + cytarabine	26.4	19.1 to 34.2	64.3	55.2 to 72.1	71.1	62.2 to 78.2	76.8	68.1 to 83.4
IM after IFN	12.6	7.3 to 19.4	43.3	34.1 to 52.1	53.5	44.0 to 62.1	55.1	45.4 to 63.7
IM 800 mg/day	45.6	40.2 to 50.9	64.4	58.4 to 69.7	71.5	64.5 to 77.4	NA	
$MR^{4.5}$ by therapy								
IM 400 mg/day	20.9	16.6 to 25.6	40.5	34.7 to 46.2	55.6	48.9 to 61.7	62.3	54.5 to 69.1
IM + IFN	21.5	17.2 to 26.1	41.5	35.8 to 47.1	58.7	52.1 to 64.6	68.8	61.1 to 75.2
IM + cytarabine	9.5	5.2 to 15.4	37.0	28.5 to 45.6	50.9	41.5 to 59.5	61.4	51.5 to 69.8
IM after IFN	5.9	2.4 to 11.6	26.8	18.6 to 35.8	44.5	34.5 to 54.0	54.5	43.0 to 64.7
IM 800 mg/day	24.1	19.6 to 28.8	50.5	44.3 to 56.3	66.2	56.9 to 73.9	NA	
MR^4 and $MR^{4.5}$, all patients								
MR^4	35.6	32.9 to 38.3	60.4	57.4 to 63.2	69.8	66.8 to 72.7	75	71.5 to 78.1
$MR^{4.5}$	19.4	17.2 to 21.7	41.9	38.9 to 44.8	57.1	53.7 to 60.3	65.6	61.7 to 69.2

Abbreviations: IFN, interferon alfa; IM, imatinib; MR, molecular response; NA, not available.

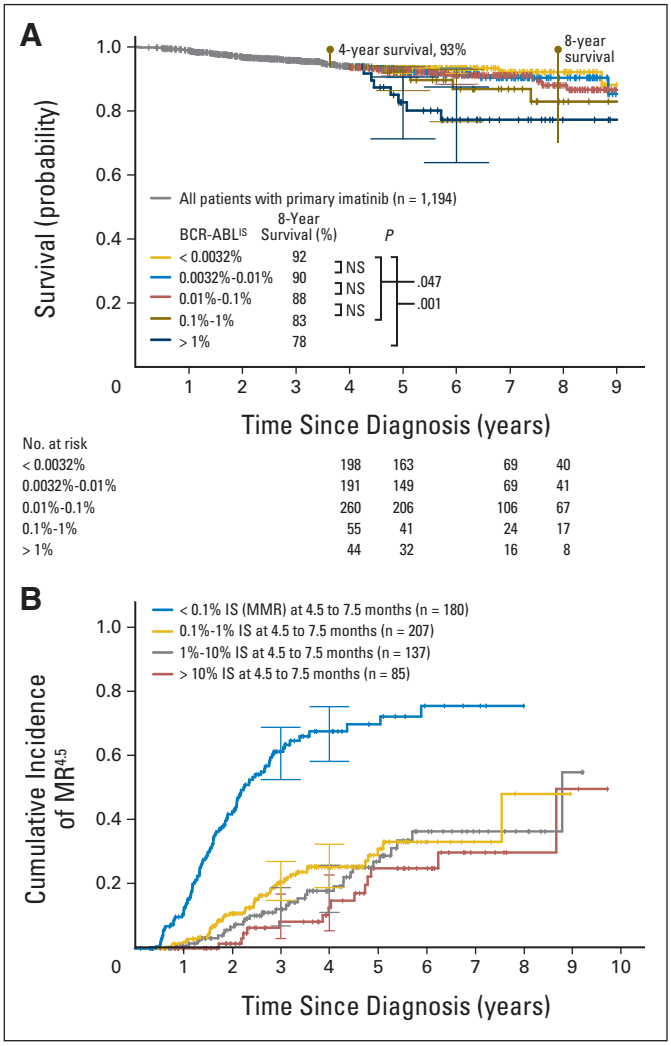

Fig 3. (A) Prognostic impact of confirmed deep molecular response (MR-[sup]4.5) at 4 years compared with lower response levels. The significance levels were for $MR^{4.5}$ versus 0.1% to 1% international scale (IS) corresponding to complete cytogenetic remission ($P = .047$), for $MR^{4.5}$ versus > 1% IS ($P = .001$), for $MR^{4.5}$ versus no $MR^{4.5}$ ($P = .047$), for 0.01% to 0.1% IS corresponding to MMR and for 0.0032% to 0.01% IS corresponding to MR^4 versus $MR^{4.5}$ and versus 0.1% to 1% IS (not statistically significant). (B) Incidence of $MR^{4.5}$ dependent on level of molecular response at 6 months. By 6 months, 21 patients had died, experienced progression, or reached $MR^{4.5}$ and were excluded from analysis (Table 3).

0.684; 95% CI, 0.544 to 0.859; $P = .001$) versus imatinib 400 mg/day (HR = 0.735; 95% CI, 0.599 to 0.917; $P = .006$) versus imatinib plus IFN (HR = 0.537; 95% CI, 0.402 to 0.718; $P < .001$) versus imatinib plus cytarabine (HR = 0.469; 95% CI, 0.338 to 0.650; $P < .001$) versus imatinib after IFN failure were significantly predictive of $MR^{4.5}$.

DISCUSSION

Deep molecular responses have gained interest because they provide a rational approach to treatment discontinuation[2,3] and may predict survival. Molecular responses at the MMR level have long been known to be associated with lower relapse rates and led to the "safe haven" concept.[4] The proportion of patients that attain $MR^{4.5}$ and the time needed to reach this response level are not well known. It is not known

Table 3. Progressions According to Response Level

Response	Observation Time (years)	5-year Survival (%)	No. Deaths	No. Progressions
CCR	4.7	94	47	13
MMR	4.5	95	42	9
MR^4	3.8	97	17	1
$MR^{4.5}$	3.0	97	6	0

Abbreviations: CCR, complete cytogenetic remission; MMR, major molecular remission; MR, molecular response.

either whether $MR^{4.5}$ can predict survival better than CCR, the current standard for survival prediction. Another important issue is the reliability of molecular testing.[15,16]

The $MR^{4.5}$ incidence reported here reaches a high level (70% after 9 years), indicating that deep molecular responses can be achieved in the majority of patients if imatinib is administered for long enough. The reliability of the molecular tests was achieved by testing according to IS in standardized laboratories only[16] and by stringent quality criteria.[15] Only values confirmed by at least one consecutive analysis were used for prediction of survival.

Forty-six percent of our patients achieved confirmed $MR^{4.5}$ after 8 years. This is higher than the stable undetectable $MR^{4.5}$ rate of 36.5% reported in another study.[5] This study used undetectable $MR^{4.5}$ of at least 2 year in duration, whereas we used $MR^{4.5}$ as determined by at least two consecutive analyses and included BCR-ABL positive patients with levels of at least $MR^{4.5}$ or less. Our definition gives a larger proportion of patients the chance for treatment discontinuation. Published data suggest that approximately 40% of the 46% with confirmed $MR^{4.5}$ (18% of all patients) potentially remain in unmaintained remission and might be considered cured of CML.[2,3]

Our observation that confirmed that $MR^{4.5}$ at 4 years predicted survival significantly better than the response level of 0.1% to 1% IS, which corresponds to CCR (8-year OS, 92% with $MR^{4.5}$ *v* 83% with 0.1% to 1% IS), is novel and identifies $MR^{4.5}$ as a predictor of survival. Because of the limited number of observed events, no verification by splitting the file into learning and validation sets was possible. Confirmation by others is therefore needed. No patient with $MR^{4.5}$, however, has experienced progression compared with 13 patients with CCR, nine with MMR, and one with MR.[4] $MR^{4.5}$ is the first molecular marker shown to be more predictive of long-term survival than is CCR. It better identifies patients who can expect a survival advantage independent of treatment. This observation lends support to the concept that TKI can cure CML if treatment is long enough and sufficiently low response levels are reached.

That early MMR predicted $MR^{4.5}$ was expected and confirms earlier observations.[4,22] MMR at 3 and 6 months resulted in earlier and higher cumulative incidences of $MR^{4.5}$ up to 83% and 69% at 5 years, whereas later MMR (after 12 or 18 months) and response-levels higher than MMR (0.1% to 1%, 1% to 10% and > 10% IS) are associated with later achievement of $MR^{4.5}$ and lower $MR^{4.5}$ incidences. This is in line with the notion that early and rigorous reduction of BCR-ABL prevents progression and provides a survival advantage.[23] It lends support to the new European LeukemiaNet recommendations to change treatment in the case of insufficient molecular response at 6 months.[24] We could not confirm female sex as a strong

Table 4. Cumulative Incidence of $MR^{4.5}$ Depending on Response-Levels at 3, 6, 12, and 18 Months

IS Response Level	Patients at Risk (No.)	Cumulative Incidence of $MR^{4.5}$					
		3 Years		4 Years		5 Years	
		%	95% CI	%	95% CI	%	95% CI
3 months (range, 1.5-4.5 months)							
> 10%	203	10.2	6.1 to 15.6	16.7	11.1 to 23.2	22.1	15.5 to 29.5
1%–10%	269	16.1	11.7 to 21.2	21.1	15.9 to 26.8	30.8	24.2 to 37.6
0.1%–1%	169	32.1	24.6 to 39.8	43.8	34.9 to 52.2	52.9	43.0 to 61.8
< 0.1%	28	64.3	43.0 to 79.4	83.3	60.0 to 93.7	83.3	60.0 to 93.7
Total	669						
6 months (range, 4.5-7.5 months)							
> 10%	85	4.6	1.2 to 11.7	8.3	3.1 to 17.0	20.1	10.2 to 32.3
1%–10%	137	8.8	4.5 to 14.9	16.7	10.1 to 24.6	21.9	14.1 to 30.8
0.1%–1%	207	14.5	9.8 to 20.1	20.3	14.5 to 26.8	28.8	21.0. to 37.2
< 0.1%	180	46.9	38.9 to 54.4	55.5	47.0 to 63.2	69.2	59.5 to 77.1
Total	609						
12 months (range, 10.5-13.5 months)							
> 10%	21	0.0		9.8	0.7 to 38.1	21.6	4.0 to 53.8
1%–10%	55	4.8	0.9 to 15.3	10.9	3.7 to 15.3	15.4	5.8 to 32.4
0.1%–1%	128	1.7	0.1 to 4.7	9.2	3.8 to 16.0	14.5	7.0 to 23.4
< 0.1%	226	38.1	24.8 to 38.6	44.2	30.9 to 45.6	56.7	42.7 to 60.8
Total	430						
18 months (range, 16.5-19.5 months)							
> 10%	12	0.0		0.0		22.9	1.3 to 60.8
1%–10%	20	7.7	0.5 to 29.2	7.7	0.5 to 29.2	7.7	0.5 to 29.2
0.1%–1%	80	1.3	0.1 to 6.2	3.5	0.6 to 11.0	6.0	1.5 to 15.3
< 0.1%	212	26.4	20.6 to 32.5	39.0	31.9 to 36.0	51.1	42.1 to 59.3
Total	324						
Patients excluded from analysis because they already had $MR^{4.5}$ or had experienced progression or died							
Months	3		6		12		18
$MR^{4.5}$	0		2		24		69
Death or progression	8		19		33		50

NOTE. In total, 1,035 (87%) of 1194 assessable patients had at least one molecular analysis during the period 3-18 months.
Abbreviations: IS, international scale; MR, molecular response.

predictor of $MR^{4.5}$, but found a trend (median time to $MR^{4.5}$, 57 months for female and 60.5 months for male patients; $P = .083$).

Because early and deep responses predict $MR^{4.5}$ and because confirmed $MR^{4.5}$ predicts survival, therapies associated with early and deep responses, such as imatinib 800 mg/day or second-generation TKI,[25,26] are of particular interest. Our observation that $MR^{4.5}$ was reached earlier and more quickly by optimized high-dose imatinib extends our earlier report of significantly faster responses with high-dose imatinib. This is different from another study restricted to younger patients ≤ 75 years old[27] and a study on high-risk patients only,[28] but is in line with early and current observations by others who report faster and higher cytogenetic and molecular response rates with imatinib 800 mg/day.[29-32] This is important for countries where second-generation TKI are not approved or not available because of high costs.[33] The median imatinib-dose in the imatinib-800 mg/day arm reached a maximum after 6 months (661 mg/day), and thereafter declined over the next 30 months to a median of 400 mg/day from year 4 onward. Apparently, less than 800 mg/day of imatinib, but clearly more than 400 mg/day applied early in the course of treatment, are needed to result in the superior response rates.

Survival was with 90% at 5 years and 86% at 8 years, similar to, and possibly better than reported for the IRIS study,[34] although no patient was removed from the study when imatinib was discontinued. The switch to second-generation TKI in 246 patients and SCT in 113 patients may have improved response after imatinib failure in a proportion of patients, but had no major influence on survival of the total study population as shown by an increase of 6-year survival from 88% to 92% after censoring for second-generation TKI and SCT. In view of a possible role of IFN in future combination therapy of CML[35] it is interesting that the faster achievement of $MR^{4.5}$ with imatinib 800 mg/day did not reach statistical significance compared with imatinib plus IFN.

We conclude that $MR^{4.5}$ is achieved by the majority of patients treated with imatinib and predicts survival better than a lower molecular response level corresponding to CCR. Predictors of $MR^{4.5}$ include optimized high-dose imatinib and early MMR. $MR^{4.5}$ is a new molecular risk predictor that identifies candidates for treatment discontinuation and may play an important role in the future path to cure CML.

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