

From the Department of Hematology/Oncology, L. and A. Seràgnoli, University of Bologna; Division of Hematology, University Federico II, Naples; and Department of Clinical and Biological Sciences, University of Turin at Orbassano, Turin, Italy; Department of Haematology, Hammersmith Hospital; and Department of Haematology, Imperial College, London, United Kingdom; Hematology Department, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; Department of Hematology, University Hospital, Basel, Switzerland; CIC 802 INSERM, CHU de Poitiers, Poitiers, France; Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI; Institute of Medical and Veterinary Science, Adelaide, South Australia, Australia; Department of Medicine and Cancer Research Center, University of Chicago, Chicago, IL; Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; Department of Hematology, University Hospital, Uppsala, Sweden; New York Presbyterian-Weill Cornell Medical Center, New York, NY; Department of Leukemia, M. D. Anderson Cancer Center, Houston, TX; Department of Medicine, Division of Hematology and Medical Oncology, Oregon Health and Science University Knight Cancer Institute, Portland, OR; Department of Hematology and Oncology, University of Leipzig, Leipzig; Universitätsklinikum Jena, Jena; and Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany.

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Corresponding author: Michele Baccarani, MD, Department of Hematology-Oncology, L. and A. Seràgnoli, S. Orsola-Malpighi Hospital, Via Massarenti 9, 40138 Bologna, Italy; e-mail: michele.baccarani@unibo.it.

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## Chronic Myeloid Leukemia: An Update of Concepts and Management Recommendations of European LeukemiaNet

Michele Baccarani, Jorge Cortes, Fabrizio Pane, Dietger Niederwieser, Giuseppe Saglio, Jane Apperley, Francisco Cervantes, Michael Deininger, Alois Gratwohl, François Guilhot, Andreas Hochhaus, Mary Horowitz, Timothy Hughes, Hagop Kantarjian, Richard Larson, Jerald Radich, Bengt Simonsson, Richard T. Silver, John Goldman, and Rudiger Hehlmann

### A B S T R A C T

#### Purpose

To review and update the European LeukemiaNet (ELN) recommendations for the management of chronic myeloid leukemia with imatinib and second-generation tyrosine kinase inhibitors (TKIs), including monitoring, response definition, and first- and second-line therapy.

#### Methods

These recommendations are based on a critical and comprehensive review of the relevant papers up to February 2009 and the results of four consensus conferences held by the panel of experts appointed by ELN in 2008.

#### Results

Cytogenetic monitoring was required at 3, 6, 12, and 18 months. Molecular monitoring was required every 3 months. On the basis of the degree and the timing of hematologic, cytogenetic, and molecular results, the response to first-line imatinib was defined as optimal, suboptimal, or failure, and the response to second-generation TKIs was defined as suboptimal or failure.

#### Conclusion

Initial treatment was confirmed as imatinib 400 mg daily. Imatinib should be continued indefinitely in optimal responders. Suboptimal responders may continue on imatinib, at the same or higher dose, or may be eligible for investigational therapy with second-generation TKIs. In instances of imatinib failure, second-generation TKIs are recommended, followed by allogeneic hematopoietic stem-cell transplantation only in instances of failure and, sometimes, suboptimal response, depending on transplantation risk.

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### INTRODUCTION

Nearly a decade has passed since the introduction into clinical practice of the first tyrosine-kinase inhibitor (TKI), imatinib mesylate, (Gleevec, Glivec; Novartis, Basel, Switzerland).<sup>1,2</sup> Before imatinib, the therapy of Philadelphia-positive (Ph+) chronic myeloid leukemia (CML) included hydroxyurea, interferon alfa (IFN- $\alpha$ ), and allogeneic hematopoietic stem-cell transplantation (alloHSCT).<sup>3</sup> The advent of imatinib, which specifically targeted the TK activity of the oncogenic proteins encoded by *BCR/ABL1*,<sup>4</sup> rapidly and dramatically modified the treatment of CML and led to important changes in management.<sup>5</sup> Subsequently, more information became available about imatinib therapy as a result of experience with more patients, longer follow-up, and better understanding of the causes and mechanisms of resistance to imatinib.<sup>6-14</sup> At the same time, other drugs, most of them also

classifiable as TKIs, were developed.<sup>15-20</sup> Some have been tested in clinical trials, and two of them, dasatinib (Sprycel; Bristol-Myers Squibb, New York, NY) and nilotinib (Tasigna; Novartis), have been registered worldwide for the treatment of patients with imatinib-intolerant and imatinib-resistant disease.<sup>21-29</sup> The confirmation of the high efficacy of imatinib, the observation that the response to imatinib is durable, and the availability of two potent new agents have raised the level of satisfaction and expectation for the outcome of therapy of CML, so that the goal of therapy has become more ambitious—an aim for 100% survival and a normal quality of life. For these reasons, the European LeukemiaNet (ELN) decided to review recent results of therapy, standard monitoring procedures, and definitions of responses and to update the published recommendations, with the aim of contributing to optimize and standardize the management of CML.

## METHODS

The relevant papers that appeared after the publication of the original ELN recommendations,<sup>5</sup> up to February 2009, were identified through the Medline database and were comprehensively and critically reviewed. With few exceptions, only papers published after 2005 were referenced. The panel also reviewed relevant abstracts presented at the 2008 meetings of the European Hematology Association and the American Society of Hematology. Four panel meetings were held between December 2007 and December 2008. Treatment recommendations were limited to the three registered TKIs (ie, imatinib, dasatinib, and nilotinib) and alloHSCT. Response definitions and treatment recommendations were based on hematologic response (HR), cytogenetic response (CgR), and molecular response (MoR) (Table 1), because these response levels are measures of leukemic cell burden and are early surrogate markers of survival.<sup>5</sup> Whenever possible, prognostic evaluations and treatment recommendations also were based on overall survival (OS), survival free from progression (ie, progression-free survival [PFS]) to accelerated phase (AP) or blast phase (BP), and event-free survival (EFS), for which the events were response loss, progression, or death. For risk assessment, Sokal<sup>30</sup> and Hasford<sup>31</sup> classifications were used throughout.

### Summary and Update of Imatinib Clinical Results

The International Randomized Study of IFN versus STI571 (IRIS) established the superiority of imatinib 400 mg daily compared with IFN- $\alpha$  and low-dose cytarabine (AraC) regarding the rate of HR, CgR, and MoR, and the study suggested a substantial advantage in PFS and OS.<sup>2,32</sup> This advantage was confirmed in subsequent reports.<sup>33,34</sup> The most comprehensive source of

information about the value of initial imatinib therapy for patients early chronic phase (ECP) disease is the IRIS trial, including published reports<sup>35,36</sup> and yearly presentations at major international meetings. With a follow-up of 7 years, imatinib was discontinued for adverse events in 5% of patients, for lack of efficacy in 15% of patients, and for other reasons in 20% of patients.<sup>37</sup> Seventy-five percent of patients with complete CgRs (CCgRs) have maintained the response so far.<sup>37</sup> The 6-year EFS, PFS, and OS rates were 83%, 93%, and 88%, respectively. All the curves showed a tendency to plateau, as—from the fourth year onward—the yearly event rate ranged between 0.3% and 2.0%.<sup>37</sup> Results similar to those of the IRIS trial were reported from the prospective, multicenter, German CML IV study, which had a 5-year OS of 94% and a 2-year EFS of 80%.<sup>38</sup> An observational, single-center, single-arm study of 204 patients with ECP disease treated with imatinib 400 mg daily indicated a complete HR (CHR) and a CCgR in 98% and 78% of patients, respectively, and a 50% major MoR (MMoR).<sup>39</sup> With a median follow-up of 38 months, 74% of patients remained on imatinib. The projected 5-year PFS and OS rates were 82% and 83%, respectively, and the survival free from any event, including imatinib discontinuation for adverse events, was 63%.<sup>39</sup> Another small, population-based, observational study reported that the CCgR at 1 year was only 44%.<sup>40</sup>

### Dose Issues

Several single-arm studies have addressed the issue of whether beginning treatment with an imatinib dose greater than 400 mg daily, or increasing imatinib dose during treatment, may improve treatment results.<sup>5,41-44</sup> In particular, the most recent analysis indicates that increasing imatinib dose is more effective in case of cytogenetic failure than in case of hematologic failure.<sup>43</sup> Data from one single-arm study, which tested an initial imatinib dose of 600 mg daily with dose escalation to 800 mg in case of suboptimal response, have been reported and have indicated that, at 12 and 24 months, the CCgR rate was 88% and 90%, respectively, and the MMoR rate was 47% and 73%, respectively.<sup>45</sup> Preliminary results of three prospective trials that tested different initial doses also have been reported. Early data from the French Spirit Study show a borderline superiority of imatinib 600 mg compared with 400 mg at 12 months, with a CCgR rate of 65% versus 57% for the 600 mg and 400 mg doses, respectively, and an MMoR rate of 52% versus 40%, respectively.<sup>46</sup> A Novartis-sponsored study, in which 476 patients were assigned to receive either imatinib 400 or 800 mg, showed a significant superiority for 800 mg on the MMoR rate at 3 months (3% v 12%), 6 months (17% v 34%), and 9 months (33% v 45%) but not at 12 months (40% v 46%).<sup>47</sup> An ELN study of 216 patients, all high risk according to Sokal,<sup>30</sup> did not show a significant superiority of imatinib 800 mg compared with 400 mg in the CCgR and MMoR rates at 12 months (64% v 58%, respectively, for CCgR; 40% v 33%, respectively, for MMoR).<sup>48</sup> The follow-up of these studies is far too short to evaluate a relationship between the initial dose and survival.

### Combination With Other Agents

Imatinib is being tested in combination with IFN- $\alpha$  and AraC. The update of a single-arm study of imatinib 400 mg daily and pegylated IFN- $\alpha$ -2b has been reported.<sup>49</sup> Although 50% of patients had discontinued IFN after 1 year and 87% had after 2 years, 62 (81%) of 76 patients were in continuous CCgR after 5 years, and 61 (80%) of 76 patients were in MMoR.<sup>49</sup> The first interim analysis of the French Spirit Study, in which 636 patients with ECP disease were assigned to receive imatinib 400 mg or 600 mg, or to receive 400 mg with a pegylated IFN- $\alpha$ -2a, or to receive 400 mg with low-dose AraC, reported the best response in the arm with imatinib plus IFN- $\alpha$ , with a 12-month CCgR of 71% versus 57% for imatinib 400 alone, and a 12-month MMoR rate of 61% versus 40% for imatinib 400 alone. However, 46% of the patients discontinued IFN- $\alpha$  during the first year of therapy.<sup>46</sup> A single-arm trial that tested different imatinib doses in combination with different AraC doses, resulted in a 3-month CCgR rate of 40%, whereas the 12-month actuarial probabilities of achieving a CCgR, a MMoR, and a complete MoR (CMoR) were 63%, 46%, and 13%, respectively.<sup>50</sup>

### Resistance and BCR-ABL1 Kinase Domain Mutations

The causes of imatinib resistance have been extensively and recently reviewed.<sup>8-10,14,51-54</sup> It has been confirmed that, in the advanced phases, resistance frequently is associated with point mutations, whereas they occur in less

**Table 1.** Definitions of Hematologic, Cytogenetic, and Molecular Response

Response by Type	Definitions
<b>Hematologic</b>	
Complete (CHR)	WBC < $10 \times 10^9/L$ Basophils < 5% No myelocytes, promyelocytes, myeloblasts in the differential Platelet count < $450 \times 10^9/L$ Spleen nonpalpable
<b>Cytogenetic*</b>	
Complete (CCgR)	No Ph+ metaphases
Partial (PCgR)	1% to 35% Ph+ metaphases
Minor (mCgR)	36% to 65% Ph+ metaphases
Minimal (minCgR)	66% to 95% Ph+ metaphases
None (noCgR)	> 95% Ph+ metaphases
<b>Molecular†</b>	
Complete (CMoR)	Undetectable <i>BCR-ABL</i> mRNA transcripts by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > $10^4$ )
Major (MMoR)	Ratio of <i>BCR-ABL</i> to <i>ABL</i> (or other housekeeping genes) $\leq 0.1\%$ on the international scale

Abbreviations: CHR, complete hematologic response; CCgR, complete cytogenetic response; PCgR, partial cytogenetic response; Ph+, Philadelphia chromosome positive; mCgR, major cytogenetic response; minCgR, minor cytogenetic response; noCgR, no cytogenetic response; CMoR, complete molecular response; PCR, polymerase chain reaction; MMoR, major molecular response.

\*If marrow cell metaphases cannot be obtained or evaluated by chromosome banding analysis, the definition of CCgR may be based on interphase fluorescent in situ hybridization of blood cells, provided that it is performed with *BCR-ABL1* extrasignal, dual color, dual fusion, or in situ hybridization probes and that at least 200 nuclei are scored. In many studies, PCgR and CCgR are counted together and reported as mCgR.

†For a standardized assessment of the MoR, the conversion of each laboratory data to the international scale is recommended, to correct for the variability of the assays in different laboratories. To allow for intralaboratory variations, a fluctuation of less than one log requires confirmation.

than 50% of patients in whom imatinib fails in chronic phase (CP).<sup>54-59</sup> Although the occurrence of a mutation usually predicts for relapse,<sup>56-61</sup> a mutation may occur also in a minority of patients in CCgR without being followed by relapse.<sup>62,63</sup> The poorer outcome of patients with P-loop mutations remains controversial,<sup>55,56,59</sup> whereas the T315I mutation is confirmed as a marker of failure for all the available TKIs.<sup>59-61,64-66</sup> The inhibitory effect of the major TKIs on *BCR-ABL* mutants has been tested in vitro. A summary of the data from 10 different studies is reported in Table 2. Mutations currently are quantified by direct sequencing, and sensitivity ranges between 10% and 25%.<sup>55,80-82</sup> Direct sequencing may be preceded by denaturing high-performance liquid chromatography that is slightly more sensitive (1% to 10%).<sup>58,82,83</sup> Other methods can identify specific mutations with a much higher sensitivity, but it is believed that the detection of a small, mutated clone is not clinically relevant.<sup>59,10,14,53,63,84</sup> The development of new mutations is a recognized cause of resistance also to second-generation TKIs. The nature of mutations may be different with dasatinib, for which T315I and F317L muta-

tions are reported more frequently, than with nilotinib, for which T315I, E255K/V, and Y253H are more common.<sup>60,61,64,65,85,86</sup>

### Treatment Discontinuation and Interruption

Discontinuation of imatinib is an appealing consequence of successful treatment, but the number of patients who achieve a stable CMoLR is still small. Six of 12 patients who were in CMoLR for more than 2 years did not experience relapse at 9 to 24 months after imatinib discontinuation; they had been pretreated with IFN- $\alpha$ . Conversely, the six patients who experienced relapse had been treated only with imatinib.<sup>87</sup> Two subsequent reports, both with short follow-up, confirmed that most relapses occur early but did not show significant differences according to prior exposure to IFN (29% in IFN-pretreated patients v 43% in those who were IFN naïve).<sup>88,89</sup> Treatment interruption should be considered to permit a safe pregnancy for a patient in MMoLR.<sup>90</sup>

### Summary and Update of AlloHSC

The assessment of the long-term outcome of alloHSC from HLA-identical siblings is still based on the data collected by the International and the European Registries between 1978 and 1997.<sup>91,92</sup> These results encompassed a period of 15 to 20 years that had survival rates of 50% and 34%, respectively. The transplantation risk score proposed by the European Blood and Bone Marrow Transplantation Group in 1998<sup>93</sup> and validated by the Center for International Bone Marrow Transplant Research in 2004<sup>94</sup> has not undergone any substantial modification (Table 3).

Prior treatment with imatinib does not affect negatively the outcome of alloHSC.<sup>95-97</sup> This has not yet been clearly established for pretreatment with dasatinib or nilotinib, although preliminary data do not suggest an increase of transplant-related toxicity in patients pretreated with these agents.<sup>98,99</sup>

### Summary of Dasatinib

Dasatinib, a piperazinyl derivative that targets many TKs, was selected for its potent inhibitory activity against *SRC* and *ABL* kinases, including the active conformation of *BCR-ABL* and most mutated forms<sup>15,16,19</sup> (Table 1). The drug was shown to be effective for the treatment of Ph+ leukemias<sup>21</sup> and was registered for the treatment of patients with imatinib-intolerant and imatinib-resistant disease who have Ph+ CML in CP, AP, and BP. A prospective, randomized study of four different doses and schedules identified a dose of 100 mg once daily as effective and better tolerated than other doses and schedules.<sup>24</sup> In patients with imatinib-intolerant disease in CP, the major CgR (MCgR) and the CCgR rates were 76% and 75%, respectively, in one study<sup>22,23</sup> and were 71% and 63%, respectively, in another.<sup>24</sup> The median time to MCgR was 2.8 months.<sup>22,23</sup> In patients with imatinib-resistant disease in CP, the MCgR and the CCgR rates were 51% and 40%, respectively, in one study<sup>22,23</sup> and were 50% and 36%, respectively, in another study.<sup>24</sup> The median time to CCgR and MMoLR was 5.5 months.<sup>100-102</sup> In 80% to 90% of patients in CP,

**Table 2.** In Vitro Sensitivity of Unmutated *BCR-ABL1* and of Some More Frequent *BCR-ABL1* Kinase Domain Mutations to Imatinib, Nilotinib, and Dasatinib

<i>BCR-ABL</i> Gene Mutation	IC50 Range by Agent (ng/mL)		
	Imatinib	Nilotinib	Dasatinib
Unmutated	153-400	< 5-13	0.4-0.9
M244V	944-1,829	20.1-20.6	0.7
L248V	1,101-5,900	26-486	4.7
G250E	796 to > 11,800	25-116	0.9-4.1
Q252H	433-1,841	8-37	1.7-2.8
Y253F	1,114-5,274	30-66	0.7-1.5
Y253H	> 3,800-10,442	238-688	1.3-10
E255K	1,873 to > 5,900	63-299	2.8-6.6
E255V	3,605-5,282	96-384	3.2-5.6
D276G	677	19	1.3
E279K	1,104	19-40	1.5
V299L	319-480	13	8-9.1
F311L	283-767	12	0.7
T315I	> 3,800 to > 11,800	369 to > 5,300	69.3 to > 500
T315A	448	NA	63
F317L	620-4,425	21-48	3.7-9.1
F317V	207-295	185	27
F317C	708	NA	NA
M351T	519-2,891	4.1-20.1	0.6-0.8
E355G	1,404	NA	NA
F359V	826-1,077	48-93	1.1-1.4
F359C	708	NA	NA
V379I	590-962	27	0.4
L384M	398-1,652	21-22	2
L387M	590-649	26	1
H396R	1,032-3,186	22-29	0.7-1.5
H396P	850-2,537	22-23	0.3-1.0
F486S	1,609-5,369	17-46	2.8

NOTE. The sensitivity of *BCR-ABL1* and of the more common *BCR-ABL1* mutations is expressed by the IC50 (ie, the drug concentration that inhibited 50% of the growth in culture of mouse lymphoblastoid BaF3 cells transfected with *BCR-ABL1* and the more common mutants). The data are taken from 10 reports.<sup>16,17,67-74</sup> It is relevant to remember the plasma concentration of the drugs as follows: imatinib 400 mg once daily minimum plasma concentration mean and standard deviation, 978  $\pm$  530 ng/mL<sup>75</sup> and maximum plasma concentration range, 2,000 to 2,500 ng/mL<sup>76,77</sup>; imatinib 400 mg twice daily median concentration, 2,770 ng/mL<sup>78</sup>; nilotinib 400 mg twice daily minimum median plasma concentration, 899 ng/mL<sup>29</sup>; dasatinib 100 mg once daily minimum plasma concentration, 2.69 ng/mL and maximum plasma concentration, 66.85 ng/mL<sup>79</sup>; dasatinib 70 mg twice daily minimum plasma concentration, 3.86 ng/mL and maximum plasma concentration, 94.09 ng/mL.<sup>79</sup>

Abbreviations: IC50, 50% inhibitory concentration; NA, not available or applicable.

**Table 3.** AlloHSC Risk Factors and EBMT Risk Score

Risk Factor	Score and Description
Disease phase	0 if CP; 1 if AP; 2 if BP
Age	0 if < 20 years; 1 if 20-40 years; 2 if > 40 years
Interval from diagnosis	0 if $\leq$ 1 year; 1 if > 1 year
Donor type	0 if HLA-identical sibling; 1 in any other instance
Donor-recipient sex match	1 if female donor and male recipient; 0 for any other match

NOTE. The EBMT risk score was based on 3,142 patients treated with alloHSC between 1989 and 1997, prior to the introduction of tyrosine kinase inhibitors. For low-risk patients (ie, risk score of 0-2), the transplantation-related mortality was 31% in the original cohort; however, in a most recent cohort of patients who underwent transplantation between 2000 and 2003, transplantation-related mortality was reduced to 17%.<sup>92</sup> For the patients with a risk score of 3-4, transplantation-related mortality was approximately 50%, and it was approximately 70% for the patients with a risk score of 5-6.<sup>93</sup>

Abbreviations: AlloHSC, allogeneic hematopoietic stem-cell transplantation; EBMT, European Group for Blood and Marrow Transplantation; CP, chronic phase; AP, accelerated phase; BP, blast phase.



the responses were maintained for 2 years, the PFS was greater than 80%, and the OS was greater than 90%. In 150 patients with imatinib-resistant disease in CP, the results were superior in patients whose therapy was changed to dasatinib 70 mg twice daily compared with those in whom the imatinib dose was increased to 800 mg.<sup>25</sup> In patients with imatinib-intolerant or imatinib-resistant disease in CP, the rate of discontinuation of dasatinib for adverse events ranged between 4% at 100 mg once daily<sup>24</sup> and 13% at 70 mg twice daily.<sup>22-23</sup> A pilot study of 45 patients in CP treated first line with dasatinib has reported a 6-month CCGR rate of 93%.<sup>103</sup>

### Summary of Nilotinib

Nilotinib is an aminopyrimidine derivative that inhibits the TK activity of the unmutated and most mutated forms of *BCR-ABL1* more potently and more selectively than imatinib<sup>17,18,26-29</sup> (Table 1). Nilotinib is effective for the treatment of Ph+ leukemias<sup>26</sup> and was registered for treating imatinib-intolerant and imatinib-resistant patients with Ph+ CML in CP and in AP at a dose of 400 mg twice daily. In 194 patients in CP who had imatinib-resistant disease, the MCGR and the CCGR rates were 48% and 30%, respectively, whereas the respective rates were 47% and 35% in those who had imatinib-intolerant disease.<sup>27</sup> For all patients in CP, 1-year OS was 95%, and the proportion of patients remaining in MCGR after 1 year was 96%.<sup>27</sup> In patients in CP, the rate of nilotinib discontinuation for adverse events was 15% overall.<sup>27</sup> The median time to MCGR was slightly less than 3 months.<sup>104</sup> Two pilot studies of 73 and 49 patients in CP, respectively, who were treated first line with nilotinib, have reported a 6-month and 12-month CCGR rate of 96%.<sup>104,105</sup>

### Prognostic Factors

**Imatinib first line, baseline prognostic factors.** The prognostic classifications proposed by Sokal<sup>30</sup> and by Hasford<sup>31</sup> (Table 4) remain valid for imatinib treatment. In the IRIS study, the CCGR rates at 12 months were 78%, 68%, and 51% for low-, intermediate-, and high-risk patients, respectively, according to Sokal<sup>32</sup>; and the MMolR rates among CCGRs were 66%, 45%, and 38%, respectively.<sup>32</sup> The 6-year OS, PFS, and EFS rates were 94%, 97%, and 91%, respectively, for low-risk patients; 87%, 92%, and 81% for intermediate-risk patients, respectively; and 76%, 83%, and 64% for high-risk patients, respectively.<sup>36</sup> These differences all were significant ( $P \leq .002$ ).<sup>36</sup> Importantly, once a CCGR was achieved, the outcome was not significantly affected by pretreatment risk score, and the reported PFS rates for CCGRs were 99%, 95%, and 95%, respectively ( $P = .20$ ).<sup>35</sup> These IRIS data have been confirmed by at least two independent studies.<sup>48,106</sup> The detection of a deletion of the long arm of chromosome 9 has not been confirmed as a significant prognostic factor (Castagnetti et al, submitted for publication).<sup>107</sup> Variant translocations, which occur in 4% to 8% of patients, were not prognostically significant in imatinib-treated patients.<sup>108,109</sup> Other clonal chromosome abnormalities in Ph+ cells (CCA/Ph+) may be detected in 5% to 10% of patients at diagnosis, for whom they predict significantly for shorter PFS and OS.<sup>106</sup> The prognostic value of gene expression profile studies that identify differential regulation of specific genes in Ph+ cells remains undetermined.<sup>110-115</sup>

**Imatinib first line, response-related prognostic factors.** In the few patients who failed to achieve a CHR after 3 months of imatinib therapy, the probability of subsequently achieving a CCGR was small ( $P = .0003$ ), and 5-year OS and

PFS rates were significantly shorter (60% and 56%, respectively;  $P = .003$  and  $0.002$ , respectively).<sup>106</sup> The few patients who remained completely Ph+ at 3 months had a low probability of achieving a CCGR later on.<sup>5,39</sup> At 6 months, patients without any CgR (Ph+ > 95%) had a low chance of achieving subsequent CCGR (25%) and MMolR (12%),<sup>39,116</sup> and patients who achieved a CCGR or partial CgR (PCGR) had a significantly better 5-year PFS, EFS, and OS.<sup>36,117</sup> At 12 months, a CCGR yielded superior results compared with a PCGR for 5-year PFS and OS,<sup>35,39,118</sup> and a PCGR was always better than a less than PCGR.<sup>35,117</sup> After 18 months of imatinib therapy, the PFS (99%) and the OS (98%) of CCGRs were always superior to those of PCGRs (87% and 76%, respectively).<sup>35,39,117</sup> The exact value of MolR was more difficult to assess. The first analysis of the IRIS study indicated that achieving a MMolR at 12 months predicted a better PFS,<sup>32</sup> but the difference became of border-line significance (5-year PFS 100% v 98%;  $P = .11$ ) in a subsequent report<sup>35</sup>; in the most recent update of the same trial, it was reported that an MMolR predicted for a better 6-year EFS (98% v 88%;  $P = .01$ ) at 18 months but not at 12 months (94% v 93%).<sup>118</sup> Other independent studies have provided similar data and have reported that PFS and OS were slightly superior for the patients who were in MMolR at 12 or 18 months; however, the difference was sometimes significant<sup>119-122</sup> and sometimes not.<sup>106,117</sup> Some reports emphasized the value of the MolR at 3 and 6 months.<sup>45,121,122</sup> Others indicated that, once a CMolR has been achieved, relapses are exceedingly rare.<sup>117,120,121</sup>

Any loss of CHR or CCGR predicted shorter PFS ( $P \leq .001$ ), and OS ( $P \leq .04$ ).<sup>106</sup> The prognostic value of the loss of MMolR is controversial, but all reports agree that an increase in transcript levels warrants closer monitoring.<sup>5,39,117-124</sup>

The detection of a kinase domain mutation that employs conventional sequencing methods has a prognostic relevance, depending on the sensitivity of the mutant clone to imatinib and second-generation TKIs (Table 2).<sup>5</sup>

The occurrence of clonal chromosome abnormalities in Ph- cells (CCA/Ph-) is rare at diagnosis<sup>125</sup> but has been noted in 3.6% to 8.1% of patients treated initially or second-line with imatinib.<sup>106,126-128</sup> The prognostic value of CCA/Ph- is not clear, partly because the follow-up of these patients is still short.<sup>127</sup> CCA/Ph- include several different abnormalities, most frequently +8, -Y, -7 or 7q-,<sup>125-129</sup> An evolution towards acute myeloid leukemia or a myelodysplastic syndrome has been reported in less than 10% of occurrences, mainly those with -7.

**Dasatinib and nilotinib, baseline and response-related prognostic factors.** In patients with imatinib-intolerant disease, there are no data predicting the response to dasatinib or nilotinib at baseline. In these patients, the response-related prognostic factors that have been identified for imatinib may apply as well to dasatinib and nilotinib, but it should not be overlooked that the response to these drugs is more rapid.<sup>22-25,100,101,103,104</sup>

In patients with imatinib-resistant disease, it was reported that hematologic resistance, clonal progression, and mutations reduced the probability of responding to dasatinib or imatinib.<sup>23-25,130,131</sup> The role of these prognostic factors is difficult to evaluate, because the data require confirmation and the follow-up is short. Because the responses to dasatinib and nilotinib are rapid,<sup>100,101,104,105</sup> the probability of achieving a CCGR later on is small if a patient has not achieved any CgR at 3 months and a less than minor CgR at 6 months.<sup>130</sup> Also, the detection of a new mutation during the treatment with a

**Table 4.** Calculation of Relative Risk

Study	Calculation	Risk Definition by Calculation
Sokal et al, 1984 <sup>30</sup>	$\text{Exp } 0.0116 \times (\text{age in years} - 43.4) + 0.0345 \times (\text{spleen} - 7.51) + 0.188 \times [(\text{platelet count} \div 700)^2 - 0.563] + 0.0887 \times (\text{blast cells} - 2.10)$	Low risk, < 0.8; intermediate risk, 0.8-1.2; high risk, > 1.2
Hasford et al, 1998 <sup>31</sup>	$0.666 \text{ when age} \geq 50 \text{ years} + (0.042 \times \text{spleen}) + 1.0956 \text{ when platelet count} > 1,500 \times 10^9/\text{L} + (0.0584 \times \text{blast cells}) + 0.20399 \text{ when basophils} > 3\% + (0.0413 \times \text{eosinophils}) \times 100$	Low risk, $\leq 780$ ; intermediate risk, 781-1,480; high risk, > 1,480

NOTE. Calculation of relative risk found at <http://www.icsg.unibo.it/rrcalc.asp>. Age is in years. Spleen is in centimeters below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percents of peripheral blood differential. All factors must be collected prior to any treatment.

**Table 5.** Monitoring the Response to Imatinib

Response	Description of Monitoring
Hematologic	At diagnosis, then every 15 days until CHR has been achieved and confirmed, then at least every 3 months or as required
Cytogenetic	At diagnosis, at 3 months, and at 6 months; then every 6 months until a CCgR has been achieved and confirmed, then every 12 months if regular molecular monitoring cannot be assured; always for occurrences of treatment failure (primary or secondary resistance), and for occurrences of unexplained anemia, leukopenia, or thrombocytopenia
Molecular by RT-Q-PCR	Every 3 months until MMolR has been achieved and confirmed, then at least every 6 months
Molecular by mutational analysis	In occurrences of suboptimal response or failure; always required before changing to other TKIs or other therapies

NOTE. Cytogenetics should be performed by chromosome banding analysis of marrow cell metaphases until CCgR has been achieved and confirmed. Interphase fluorescent in situ hybridization cannot be used to assess a less-than-complete response, but it can substitute for chromosome banding analysis to monitor the completeness of a CCgR, provided that *BCR-ABL1* extrasignal, dual color, dual fusion, or in situ hybridization probes are used and that at least 200 nuclei are scored.<sup>135-137</sup>

Abbreviations: CHR, complete histologic response; CCgR, complete cytogenetic response; RT-Q-PCR, real-time quantitative polymerase chain reaction; MMolR, major molecular response.

second-generation TKI is important, because it is a signal of resistance or genetic instability.

### Monitoring Response to Treatment

Monitoring the response to imatinib requires blood counts and differentials, cytogenetics, and molecular testing for *BCR-ABL1* transcript level and for *BCR-ABL1* kinase domain mutations<sup>132-134</sup> (Table 5). Blood counts and differentials are required frequently during the first 3 months until a CHR has been achieved and confirmed. Cytogenetics, performed with chromosome banding analysis (CBA) of marrow cell metaphases, is required at 3 and 6 months, then every 6 months until a CCgR has been achieved and confirmed, then every 12 months if regular molecular monitoring cannot be assured, and always in instances of myelodysplastic features, suboptimal response, or failure. Marrow CBA is preferred to interphase fluorescent in situ hybridization (I-FISH), because the definition of different grades of CgR is based on CBA, and because I-FISH detects neither CCA/Ph<sup>-</sup> nor CCA/Ph<sup>+</sup>. However, once a CCgR has been achieved, if CBA of a sufficient number of marrow cell metaphases cannot be performed, or marrow cells cannot be sampled, I-FISH of blood cells can be used to monitor the completeness of CgR by using

*BCR-ABL1* extrasignal, dual color, or dual fusion probes and by scoring at least 200 nuclei.<sup>135-137</sup> Real-time, quantitative polymerase chain reaction assessment of *BCR-ABL1* transcript levels is recommended every 3 months until a MMolR has been achieved and confirmed then at least every 6 months. Real-time, quantitative polymerase chain reaction should be performed on whole buffy-coat blood cells, and results should be expressed as a ratio of *BCR-ABL* to *ABL* (or other housekeeping genes)  $\times$  100%; converted to the international scale, the ratio  $\leq$  0.1% defined MmolR.<sup>132,138-143</sup> Suboptimal responders and patients with warning features may require more frequent monitoring. Monitoring the response to other TKIs requires the same tests, but earlier and more frequent testing may be appropriate, because responses are more rapid.

### Response Definitions

On the basis of the degree of HR, CgR, and MolR, and on the basis of the time when these responses are achieved, the overall response to imatinib can be defined as optimal, suboptimal, and failure (Table 6). Optimal means that there is no indication that a change of therapy may improve a survival that is currently projected as close to 100% after 6 to 7 years. Suboptimal response

**Table 6.** Evaluation of Overall Response to Imatinib First-Line in Early Chronic Phase

Evaluation Time, Months	Response			Warnings
	Optimal	Suboptimal	Failure	
Baseline	NA	NA	NA	High risk; CCA/Ph+*
3	CHR and at least minor CgR (Ph+ $\leq$ 65%)	No CgR (Ph+ $>$ 95%)	Less than CHR	NA
6	At least PCgR (Ph+ $\leq$ 35%)	Less than PCgR (Ph+ $>$ 35%)	No CgR (Ph+ $>$ 95%)	NA
12	CCgR	PCgR (Ph+ 1% to 35%)	Less than PCgR (Ph+ $>$ 35%)	Less than MMolR†
18	MMolR†	Less than MMolR†	Less than CCgR	NA
Any time during treatment	Stable or improving MMolR†	Loss of MMolR†; mutations‡	Loss of CHR; loss of CCgR; mutations§; CCA/Ph+	Increase in transcript levels  ; CCA/Ph-

NOTE. With respect to prior recommendations,<sup>5</sup> a new definition of optimal response was introduced; an earlier definition of suboptimal response is recommended at 3 months in instances of cytogenetic resistance; an earlier definition of failure is recommended at 3 months in instances of hematologic resistance and at 6 months in instances of cytogenetic resistance; clonal progression (ie, CCA/Ph+) during treatment was identified as treatment failure; a deletion of the long arm of chromosome 9 (del9q+) is no longer recognized as a warning.

Abbreviations: NA, not applicable; CCA, clonal chromosome abnormalities; Ph+, Philadelphia chromosome positive; CHR, complete hematologic response; CgR, cytogenetic response; PCgR, partial cytogenetic response; MMolR, major molecular response; CCgR, complete cytogenetic response; Ph-, Philadelphia chromosome negative.

\*CCA/Ph+ is a warning factor at diagnosis, although its occurrence during treatment (ie, clonal progression) is a marker of treatment failure. Two consecutive cytogenetic tests are required and must show the same CCA in at least two Ph+ cells.

†MMolR indicates a ratio of *BCR-ABL1* to *ABL1* or other housekeeping genes of  $\leq$  0.1% on the international scale.

‡*BCR-ABL1* kinase domain mutations still sensitive to imatinib (Table 3).

§*BCR-ABL1* kinase domain mutations poorly sensitive to imatinib (Table 2).

||The significance of the increase may vary by a factor of 2 to 10, depending on the laboratories.

means that the patient may still have a substantial long-term benefit from continuing a specific treatment, but the chances of an optimal outcome are reduced, so that suboptimal responders may be eligible for alternative approaches. However, the condition of suboptimal response is transitory by nature. Failure means that a favorable outcome is unlikely, and that the patient should receive a different treatment whenever available and applicable. The relevance of these definitions—optimal, suboptimal, and failure—is modulated by the coexistence of warning prognostic factors. Warning means that the characteristics of the disease may adversely affect the response to that therapy and may require a more stringent and careful monitoring.

### Treatment Recommendations

Hydroxyurea still may be used only for a short period of time, or in a patient in whom a TKI is not advised. IFN- $\alpha$  is still an option in case of pregnancy, for which imatinib should not be administered either at conception or during gestation,<sup>90</sup> and in some patients, mainly low-risk patients, for whom imatinib may be not appropriate because of comorbidities or concomitant medications. Except for in patients with these exceptions, the standard treatment of CML in patients who present in CP is imatinib 400 mg daily (Table 7). For instances of intolerance, the choices are dasatinib and nilotinib. For instances of suboptimal response to imatinib, which is a transitory condition, there is no solid, confirmed evidence that a change in treatment will improve the response, but there are at least two other options—namely an increase of imatinib dose or a change to a second-generation TKIs. For patients who experience imatinib failure, particularly hematologic failure, drug therapy should be changed to dasatinib or nilotinib. The detection of some mutations may help to decide between dasatinib and nilotinib (Table 2). AlloHSCT is recommended for patients in AP or BP or with the T315I mutation and for the patients who experience failure on second-line TKIs. AlloHSCT is also a significant option in the patients who have a suboptimal response to dasatinib or nilotinib second line, particularly for instances of warnings (Table 8). Treatment recommendations are different for the patients who are referred in AP or BP. These patients should preferentially receive an alloHSCT, if eligible, after a pretreatment with imatinib 600 or 800 mg if TKI naïve, or with second-generation TKIs if imatinib resistant.

Because performing an alloHSCT requires either an HLA-identical sibling or a well-matched unrelated donor, it is recommended that the search for a donor is initiated at appropriate times, depending on the characteristics of the patients, the stage of disease, and the response to treatment (Table 9). Successful treatment with a TKI, normally, should never be discontinued. The

dose should not be reduced to less than the standard dose in the absence of significant adverse effects. Dose reduction or discontinuation may be tested only within the framework of controlled trials.

## DISCUSSION

The basis of current therapy for CML in CP is the three TKIs—imatinib, dasatinib, and nilotinib—and alloHSCT. The treatment algorithm appears simple, easy to trace, and easy to follow; imatinib is first line, dasatinib or nilotinib is second line, and alloHSCT is for instances of failure of drug therapy, and for patients in AP or BP. The role of alloHSCT is still influenced by a substantial mortality and by late morbidity, mainly because of chronic graft-versus-host disease. A partial guide to the choice of second-generation TKIs may be provided by the detection of some mutations. A few mutations appear particularly resistant to dasatinib, and others appear resistant to nilotinib (Table 2). At least one mutation (ie, T315I) is highly resistant to both. Other than mutations, clinical relevance of other differences between dasatinib and nilotinib is unknown.

Because TKIs are potent and may even be curative, and because the outcome of alloHSCT depends so much on timing, the application of a therapeutic algorithm is particularly case sensitive. One tends to consider any response less than optimal as unsatisfactory, which may rapidly translate into failure. The more ambitious the goal of therapy is, the greater the tendency to anticipate the response and to change prematurely to another treatment. However, abandoning one treatment for another, or for an investigational therapy, should always be based on meaningful and reasoned data. The boundaries between optimal response, suboptimal response, and failure are formally sharp; however, because they are sharp, it may be wise to seek confirmation by repeating appropriate tests, when the results are equivocal, before taking a therapeutic decision.

These revised and updated treatment recommendations differ from the earlier ones,<sup>5</sup> in that they define failure already at 3 months in occurrences of hematologic resistance, and they define

**Table 7.** Treatment Recommendations

Type of Disease	Recommendation
Chronic phase	
First line	
All patients	Imatinib 400 mg daily
Second line	
Imatinib intolerant	Dasatinib or nilotinib
Imatinib suboptimal response	Continue imatinib same dose; or test high dose imatinib, dasatinib, or nilotinib
Imatinib failure	Dasatinib or nilotinib; alloHSCT in the patients who have experienced progression to AP/BP and in patients who carry the T315I mutation
Third line	
Dasatinib or nilotinib suboptimal response	Continue dasatinib or nilotinib, with an option for alloHSCT in patients with warning features (ie, prior hematologic resistance to imatinib, mutations) and in patients with an EBMT risk score $\leq 2$
Dasatinib or nilotinib failure	AlloHSCT
Accelerated and blast	
First line	
Patients who are TKI naïve	AlloHSCT, preceded by imatinib 600 or 800 mg, dasatinib, or nilotinib, in case of mutations poorly sensitive to imatinib
Second line	
Patients with prior treatment of imatinib	AlloHSCT, preceded by dasatinib or nilotinib

Abbreviations: AlloHSCT, allogeneic hematopoietic stem-cell transplantation; AP, accelerated phase; BP, blast phase; EBMT, European Group for Blood and Marrow Transplantation; TKI, tyrosine kinase inhibitor.

**Table 8.** Recommendations for AlloHSCt

Time Point by Steps	Patient Population
Search for a family donor (ie, HLA-identical sibling) Initially, at diagnosis	In patients presenting in AP or BP; in children and adolescents (younger than 20 years old); in patients presenting with warning factors
At time of imatinib failure	All patients
Search for an unrelated donor, if a family donor was not found	
Initially, at diagnosis	In patients presenting in AP or BP
At time of imatinib failure	In patients who have experienced disease progression to AP or BP, who carry the T315I mutation, or who are hematologically resistant to imatinib
During or after therapy with a second-generation TKI	In all patients with TKI failure In patients with a suboptimal response to TKI and with a predictable EBMT risk score of 0-2
Perform alloHSCt	
Initially, at diagnosis	In patients presenting in AP or BP (Pretreatment with a TKI is recommended.)
At time of imatinib failure (ie, second line)	In patients who have experienced progression to AP or BP (and pretreatment with a second-generation TKI is recommended) and in patients carrying the T315I mutation
In instances of failure with second-generation TKI	In all patients

NOTE. These recommendations apply to the patients who, by age and health conditions, are considered eligible for alloHSCt, with standard or myeloablative procedures, from an HLA-identical sibling, or a matched or partially mismatched unrelated donor (ie, 8/8 or 7/8 A, B, C, DR, high resolution). Other donors and hematopoietic stem-cell sources like cord blood, and other nonstandard procedures, are still investigational and should be performed in the context of controlled trials. Also, the occurrence of a syngeneic HSCT from an identical twin is not included in these recommendations and warrants tailored decisions.

Abbreviations: AlloHSCt, allogeneic hematopoietic stem-cell transplantation; AP, accelerated phase; BP, blast phase; TKI, tyrosine kinase inhibitor; EBMT, European Group on Blood and Marrow Transplantation.

suboptimal response and failure already at 3 and 6 months, respectively, in occurrences of cytogenetic resistance. These anticipations are a consequence of the introduction of other TKIs. For that reason, it is recommended to perform the first cytogenetic examination at 3 months. The role of molecular response has not been modified, because it is not yet clear to what extent the outcome of patients in CCgR is influenced by the fluctuations of *BCR-ABL1* transcript levels, which may depend on technique but which also may be spontaneous. The most critical new recommendations that are provided in this article concern the definition of the response to second-generation TKIs as second-line therapy. They are provisional but warranted.

It is important to understand that a gray, intermediate zone exists and is influenced by statistical variability, for which a recommendation helps to make a therapeutic decision. However, the decision must rely on specifically trained and experienced personnel who are based at

a reference center. This is particularly important in occurrences of advanced disease, contrasting or unstable results, and severe or unexpected adverse effects. The balance between practice and investigation is always difficult and requires clinical experience, but clinical practice and investigation should be as one in a rare disease like CML, for which therapy and monitoring are expensive and sophisticated. The first TKI, imatinib, was defined by the metaphor of magic bullet, but imatinib and the other TKIs are not magic, and they are excellent bullets only if they are fired with a good rifle and are carefully aimed. Aiming requires monitoring, which may cost only 5% to 10% of the whole cost of treatment.<sup>132</sup> Monitoring the treatment should not be intended only for the benefit of the individual patient, and it should be performed as much as possible within the framework of controlled studies, while not forgetting that there is still space and need for investigational trials that test new agents and unexplored treatment modalities.

**Table 9.** Provisional Definition of the Response to Second-Generation TKIs, Dasatinib and Nilotinib, As Second-Line Therapy of Patients With Imatinib-Resistant Disease in Chronic Phase

Evaluation Time, Months	Response		
	Suboptimal	Failure	Warnings
Baseline	NA	NA	Hematologic resistance to imatinib; CCA/Ph+ (ie, clonal progression); mutations*
3	Minor CgR (Ph+ 36% to 65%)	No CgR (Ph+ > 95%); new mutations*	Minimal CgR (Ph+ 66% to 95%)
6	PCgR (Ph+ 1% to 35%)	Minimal CgR (Ph+ 66% to 95%); new mutations*	Minor CgR (Ph+ 36% to 65%)
12	Less than MMolR†	Less than PCgR (Ph+ > 35%); new mutations*	

NOTE. The *BCR-ABL1* transcript levels at 3 months have also been reported to be prognostically important.<sup>142</sup> The probability of achieving an MMolR later was 86% if, at 3 months, the ratio was  $\leq 1\%$ ; the probability was 55% if the ratio was 1% to 10%; and the probability was only 4% if the ratio was  $> 10\%$ . The definitions are limited to suboptimal response, failure, and warning, because it is premature to define the optimal response to these agents.

Abbreviations: TKIs, tyrosine kinase inhibitors; NA, not applicable or not available; CCA, clonal chromosome abnormalities; Ph+, Philadelphia chromosome positive; CgR, cytogenetic response; PCgR, partial cytogenetic response; MMolR, major molecular response.

\**BCR-ABL1* kinase domain mutations poorly sensitive to TKIs (Table 2).

†Ratio of *BCR-ABL1* to *ABL1* or to other housekeeping genes  $\leq 0.1\%$  on the international scale.



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## AUTHOR CONTRIBUTIONS

**Conception and design:** Michele Baccarani, Jorge Cortes, Fabrizio Pane, Dietger Niederwieser, Giuseppe Saglio, Jane Apperley, Francisco Cervantes, Michael Deininger, Alois Gratwohl, François Guilhot, Andreas Hochhaus, Mary Horowitz, Timothy Hughes, Hagop Kantarjian, Richard Larson, Jerald Radich, Bengt Simonsson, Richard T. Silver, John Goldman, Rudiger Hehlmann **Administrative support:** Michele Baccarani **Collection and assembly of data:** Michele Baccarani, Jorge Cortes, Fabrizio Pane, Dietger Niederwieser, Giuseppe Saglio, Jane Apperley, Francisco Cervantes, Michael Deininger, Alois Gratwohl, François Guilhot, Andreas Hochhaus, Mary Horowitz, Timothy Hughes, Hagop Kantarjian, Richard Larson, Jerald Radich, Bengt Simonsson, Richard T. Silver, John Goldman, Rudiger Hehlmann **Data analysis and interpretation:** Michele Baccarani, Jorge Cortes, Fabrizio Pane, Dietger Niederwieser, Giuseppe Saglio, Jane Apperley, Francisco Cervantes, Michael Deininger, Alois Gratwohl, François Guilhot, Andreas Hochhaus, Mary Horowitz, Timothy Hughes, Hagop Kantarjian, Richard Larson, Jerald Radich, Bengt Simonsson, Richard T. Silver, John Goldman, Rudiger Hehlmann **Manuscript writing:** Michele Baccarani, Jorge Cortes, Fabrizio Pane, Dietger Niederwieser, Michael Deininger, John Goldman **Final approval of manuscript:** Michele Baccarani, Jorge Cortes, Fabrizio Pane, Dietger Niederwieser, Giuseppe Saglio, Jane Apperley, Francisco Cervantes, Michael Deininger, Alois Gratwohl, François Guilhot, Andreas Hochhaus, Mary Horowitz, Timothy Hughes, Hagop Kantarjian, Richard Larson, Jerald Radich, Bengt Simonsson, Richard T. Silver, John Goldman, Rudiger Hehlmann

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