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

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## ABSTRACT

**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 imatinb, 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).[1,2] 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).[3] The advent of imatinib, which specifically targeted the TK activity of the oncogenic proteins encoded by *BCR/ABL1*,[4] rapidly and dramatically modified the treatment of CML and led to important changes in management.[5] 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.[6-14] At the same time, other drugs, most of them also classifiable as TKIs, were developed.[15-20] 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.[21-29] 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,[5] 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 (MolR) (Table 1), because these response levels are measures of leukemic cell burden and are early surrogate markers of survival.[5] 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[30] and Hasford[31] 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 MolR, and the study suggested a substantial advantage in PFS and OS.[2,32] This advantage was confirmed in subsequent reports.[33,34] 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[35,36] 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.[37] Seventy-five percent of patients with complete CgRs (CCgRs) have maintained the response so far.[37] 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%.[37] 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%.[38] 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 MolR (MMolR).[39] 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%.[39] Another small, population-based, observational study reported that the CCgR at 1 year was only 44%.[40]

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

| Response by Type | Definitions |
|---|---|
| Hematologic | |
| 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 |
| Cytogenetic* | |
| 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 |
| Molecular† | |
| Complete (CMolR) | Undetectable *BCR-ABL* mRNA transcripts by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity $> 10^4$) |
| Major (MMolR) | Ratio of *BCR-ABL* to *ABL* (or other housekeeping genes) $\leq 0.1\%$ on the international scale |

Abbreviations: CHR, complete hematologic response; CCgR, complete cytogenic response; PCgR, partial cytogenetic response; Ph+, Philadelphia chromosome positive; MCgR, major cytogenetic response; minCgR, minor cytogenetic response; noCgR, no cytogenetic response; CMolR, complete molecular response; PCR, polymerase chain reaction; MMolR, 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 MolR, 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.

### 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.[5,41-44] In particular, the most recent analysis indicates that increasing imatinib dose is more effective in case of cytogenic failure than in case of hematologic failure.[43] 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 MMolR rate was 47% and 73%, respectively.[45] 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 MMolR rate of 52% versus 40%, respectively.[46] 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 MMolR 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%).[47] An ELN study of 216 patients, all high risk according to Sokal,[30] did not show a significant superiority of imatinib 800 mg compared with 400 mg in the CCgR and MMolR rates at 12 months (64% *v* 58%, respectively, for CCgR; 40% *v* 33%, respectively, for MMolR).[48] 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.[49] 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 MMolR.[49] 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 MMolR rate of 61% versus 40% for imatinib 400 alone. However, 46% of the patients discontinued IFN-$\alpha$ during the first year of therapy.[46] 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 MMolR, and a complete MolR (CMolR) were 63%, 46%, and 13%, respectively.[50]

### Resistance and BCR-ABL1 Kinase Domain Mutations

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

  

than 50% of patients in whom imatinib fails in chronic phase (CP).[54-59] Although the occurrence of a mutation usually predicts for relapse,[56-61] a mutation may occur also in a minority of patients in CCgR without being followed by relapse.[62,63] The poorer outcome of patients with P-loop mutations remains controversial,[55,56,59] whereas the T315I mutation is confirmed as a marker of failure for all the available TKIs.[59-61,64-66] 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%.[55,80-82] Direct sequencing may be preceded by denaturing high-performance liquid chromatography that is slightly more sensitive (1% to 10%).[58,82,83] 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.[5,9,10,14,53,63,84] 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 mutations are reported more frequently, than with nilotinib, for which T315I, E255K/V, and Y253H are more common.[60,61,64,65,85,86]

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

| *BCR-ABL* 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.[16,17,67-74] 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 ± 530 ng/mL[75] and maximum plasma concentration range, 2,000 to 2,500 ng/mL[76,77]; imatinib 400 mg twice daily median concentration, 2,770 ng/mL[78]; nilotinib 400 mg twice daily minimum median plasma concentration, 899 ng/mL[29]; dasatinib 100 mg once daily minimum plasma concentration, 2.69 ng/mL and maximum plasma concentration, 66.85 ng/mL[79]; dasatinib 70 mg twice daily minimum plasma concentration, 3.86 ng/mL and maximum plasma concentration, 94.09 ng/mL.[79]

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

### *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.[87] 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).[88,89] Treatment interruption should be considered to permit a safe pregnancy for a patient in MMolR.[90]

### *Summary and Update of AlloHSCT*

The assessment of the long-term outcome of alloHSCT from HLA-identical siblings is still based on the data collected by the International and the European Registries between 1978 and 1997.[91,92] 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[93] and validated by the Center for International Bone Marrow Transplant Research in 2004[94] has not undergone any substantial modification (Table 3).

Prior treatment with imatinib does not affect negatively the outcome of alloHSCT.[95-97] 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.[98,99]

### *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-ABL1* and most mutated forms[15,16,19] (Table 1). The drug was shown to be effective for the treatment of Ph+ leukemias[21] 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.[24] In patients with imatinib-intolerant disease in CP, the major CgR (MCgR) and the CCgR rates were 76% and 75%, respectively, in one study[22,23] and were 71% and 63%, respectively, in another.[24] The median time to MCgR was 2.8 months.[22,23] In patients with imatinib-resistant disease in CP, the MCgR and the CCgR rates were 51% and 40%, respectively, in one study[22,23] and were 50% and 36%, respectively, in another study.[24] The median time to CCgR and MMolR was 5.5 months.[100-102] In 80% to 90% of patients in CP,

**Table 3.** AlloHSCT 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 ≤ 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 alloHSCT 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%.[92] 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.[93]

Abbreviations: AlloHSCT, 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.[25] 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[24] and 13% at 70 mg twice daily.[22-23] A pilot study of 45 patients in CP treated first line with dasatinib has reported a 6-month CCgR rate of 93%.[103]

### 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[17,18,26-29] (Table 1). Nilotinib is effective for the treatment of Ph+ leukemias[26] 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.[27] For all patients in CP, 1-year OS was 95%, and the proportion of patients remaining in MCgR after 1 year was 96%.[27] In patients in CP, the rate of nilotinib discontinuation for adverse events was 15% overall.[27] The median time to MCgR was slightly less than 3 months.[104] 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%.[104,105]

### Prognostic Factors

*Imatinib first line, baseline prognostic factors.* The prognostic classifications proposed by Sokal[30] and by Hasford[31] (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[32]; and the MMolR rates among CCgRs were 66%, 45%, and 38%, respectively.[32] 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.[36] These differences all were significant ($P \leq .002$).[36] 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 ($P = .20$).[35] These IRIS data have been confirmed by at least two independent studies.[48,106] 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).[107] Variant translocations, which occur in 4% to 8% of patients, were not prognostically significant in imatinib-treated patients.[108,109] 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.[106] The prognostic value of gene expression profile studies that identify differential regulation of specific genes in Ph+ cells remains undetermined.[110-115]

*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).[106] The few patients who remained completely Ph+ at 3 months had a low probability of achieving a CCgR later on.[5,39] At 6 months, patients without any CgR (Ph+ > 95%) had a low chance of achieving subsequent CCgR (25%) and MMolR (12%),[39,116] and patients who achieved a CCgR or partial CgR (PCgR) had a significantly better 5-year PFS, EFS, and OS.[36,117] At 12 months, a CCgR yielded superior results compared with a PCgR for 5-year PFS and OS,[35,39,118] and a PCgR was always better than a less than PCgR.[35,117] 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).[35,39,117] 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,[32] but the difference became of border-line significance (5-year PFS 100% *v* 98%; $P = .11$) in a subsequent report[35]; 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%).[118] 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[119-122] and sometimes not.[106,117] Some reports emphasized the value of the MolR at 3 and 6 months.[45,121,122] Others indicated that, once a CMolR has been achieved, relapses are exceedingly rare.[117,120,121]

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

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).[5]

The occurrence of clonal chromosome abnormalities in Ph− cells (CCA/Ph−) is rare at diagnosis[125] but has been noted in 3.6% to 8.1% of patients treated initially or second-line with imatinib.[106,126-128] The prognostic value of CCA/Ph− is not clear, partly because the follow-up of these patients is still short.[127] CCA/Ph− include several different abnormalities, most frequently +8, −Y, −7 or 7q−.[125-129] 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.[22-25,100,101,103,104]

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.[23-25,130,131] 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,[100,101,104,105] 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.[130] 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[30] | Exp 0.0116 × (age in years − 43.4) + 0.0345 × (spleen − 7.51) + 0.188 × [(platelet count ÷ 700)$^2$ − 0.563] + 0.0887 × (blast cells − 2.10) | Low risk, < 0.8; intermediate risk, 0.8-1.2; high risk, > 1.2 |
| Hasford et al, 1998[31] | 0.666 when age ≥ 50 years + (0.042 × spleen) + 1.0956 when platelet count > 1,500 × $10^9$L + (0.0584 × blast cells) + 0.20399 when basophils > 3% + (0.0413 × eosinophils) × 100 | Low risk, ≤ 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.[135-137]

Abbreviations: CHR, complete histologic response; CCgR, complete cytogenic 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 reponse to imatinib requires blood counts and differentials, cytogenetics, and molecular testing for *BCR-ABL1* transcript level and for *BCR-ABL1* kinase domain mutations[132-134] (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− nor CCA/Ph+. 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.[135-137] 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) × 100%; converted to the international scale, the ratio ≤ 0.1% defined MmolR.[132,138-143] 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

| | Response | | | |
|---|---|---|---|---|
| Evaluation Time, Months | Optimal | Suboptimal | Failure | Warnings |
| Baseline | NA | NA | NA | High risk; CCA/Ph+* |
| 3 | CHR and at least minor CgR (Ph+ ≤ 65%) | No CgR (Ph+ > 95%) | Less than CHR | NA |
| 6 | At least PCgR (Ph+ ≤ 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,[5] 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 ≤ 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,[90] 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 naive, or with second-generation TKIs if imatinib resistant.

Because perfoming 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.

Becuase 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,[5] 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 T315 I 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. Aimingrequires monitoring, which may cost only 5% to 10% of the whole cost of treatment.[132] 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 | | Warnings |
|---|---|---|---|
| | Suboptimal | Failure | |
| 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.[142] The probability of achieving an MMolR later was 86% if, at 3 months, the ratio was ≤ 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 ≤ 0.1% on the international scale.

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## REFERENCES


1. Druker BJ, Talpaz M, Resta DJ, et al: Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 344:1031-1037, 2001
2. O'Brien SG, Guilhot F, Larson R, et al: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 348:994-1004, 2003
3. Silver RT, Woolf SH, Hehlmann R, et al: An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: Developed for the American Society of Hematology. Blood 94:1517-1536, 1999
4. Druker BJ, Tamura S, Buchdunger E, et al: Effects of a selective inhibitor of the ABL tyrosine kinase on the growth of BCR-ABL–positive cells. Nat Med 2:561-566, 1996
5. Baccarani M, Saglio G, Goldman J, et al: Evolving concepts in the management of chronic myeloid leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 108:1809-1820, 2006
6. Goldman JM: How I treat chronic myeloid leukemia in the imatinib era. Blood 110:2828-2837, 2007
7. Jabbour E, Cortes JE, Giles F, et al: Current and emerging treatment options in chronic myeloid leukemia. Cancer 109:2171-2181, 2007
8. Hehlmann R, Hochhaus A, Baccarani M, on behalf of the European LeukemiaNet: Chronic myeloid leukemia. Lancet 370:342-350, 2007
9. Apperley JF: Part I: Mechanisms of resistance to imatinib in chronic myeloid leukemia. Lancet Oncol 8:1018-1029, 2007
10. Apperley JF: Part II: Management of resistance to imatinib in chronic myeloid leukaemia. Lancet Oncol 8:1116-1129, 2007
11. Hehlmann R, Berger U, Pfirrmann M, et al: Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia. Blood 109: 4686-4692, 2007
12. Jabbour E, Kantarjian H: Chronic myeloid leukemia. Semin Hemat 44:S1-S150, 2007 (suppl 1)
13. Druker BJ: Translation of the Philadelphia chromosome into therapy for CML. Blood 112:4808-4815, 2008
14. Quintas-Cardama A, Cortes J: Molecular biology of BCR-ABL1–positive chronic myeloid leukemia. Blood 113:1619-1630, 2009
15. Shah N, Tran C, Lee FY, et al: Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 305:399-401, 2004
16. Burgess M, Skaggs BJ, Shah NP, et al: Comparative analysis of two clinically active BCR-ABL kinase inhibitors reveals the role of conformation-specific binding in resistance. PNAS 102:3395-3400, 2005
17. Weisberg E, Manley PW, Breitentein W, et al: Characterization of AMN107, a selective inhibitor of native and mutant BCR-ABL. Cancer Cell 7:129-141, 2005
18. Golemovic M, Verstovsek S, Giles F, et al: AMN107, a novel aminopyrimidine inhibitor of BCR-ABL, has in vitro activity against imatinib-resistant chronic myeloid leukemia. Clin Cancer Res 11:4941-4947, 2005
19. Tokarski JS, Newitt JA, Chang CYJ, et al: The structure of dasatinib (BMS-354825) bound to activated ABL kinase domain elucidates its inhibitory activity against imatinib-resistant ABL mutation. Cancer Res 66:5790-5797, 2006
20. Puttini M, Coluccia AML, Boschelli F, et al: In vitro and in vivo activity of SKI-606, a novel src-abl inhibitor, against imatinib-resistant BCR-ABL neoplastic cells. Cancer Res 66:11314-11322, 2006
21. Talpaz M, Shah PS, Kantarjian H, et al: Dasatinib in imatinib-resistant Philadelphia chromosome–positive leukemias. N Engl J Med 354:2531-2541, 2006
22. Hochhaus A, Kantarjian HM, Baccarani M, et al: Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. Blood 109:2303-2309, 2007
23. Hochhaus A, Baccarani M, Deininger M, et al: Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. Leukemia 22:1200-1206, 2008
24. Shah NP, Kantarjian HM, Kim DW, et al: Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol 26:3204-3212, 2008


  

**25.** Kantarjian H, Pasquini R, Hamerschlak N, et al: Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: A randomized phase 2 trial. Blood 109: 5143-5150, 2008

**26.** Kantarjian H, Giles F, Wunderle L, et al: Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med 354:2542-2551, 2006

**27.** Kantarjian HM, Giles F, Gattermann N, et al: Nilotinib (AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome–positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood 110:3540-3546, 2008

**28.** Plosker GJ, Robinson DM: Nilotinib. Drugs 68:449-459, 2008

**29.** Deininger MW: Nilotinib. Clin Cancer Res 14:4027-4031, 2008

**30.** Sokal JE, Cox EB, Baccarani M, et al: Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 63:789-799, 1984

**31.** Hasford J, Pfirmann M, Hehlmann R, et al: A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. J Natl Cancer Inst 90:850-858, 1998

**32.** Hughes TP, Kaeda J, Brandford S, et al: Frequency of major molecular response to imatinib or interferon alpha plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 349:1423-1432, 2003

**33.** Roy L, Guilhot J, Krahnke T, et al: Survival advantage from imatinib compared with the combination interferon alfa plus cytarabine in chronic-phase chronic myelogenous leukemia: Historical comparison between two phase 3 trials. Blood 108: 1478-1484, 2006

**34.** Kantarjian HM, Talpaz M, O'Brien S, et al: Survival benefit with imatinib mesylate versus interferon alpha–based regimens in newly diagnosed chronic-phase chronic myelogenous leukemia. Blood 108:1835-1840, 2006

**35.** Druker BJ, Guilhot F, O'Brien SO, et al: Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 355:2408-2417, 2006

**36.** Hochhaus A, O'Brien SG, Guilhot F, et al: Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia 23:1054-1061, 2009

**37.** O'Brien SG, Guilhot F, Goldman J, et al: International randomized study of interferon versus STI571 (IRIS) 7-year follow-up: Sustained survival, low rate of transformation and increased rate of major molecular response (MMR) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib (IM). Blood 112:76, 2008 (abstr 186)

**38.** Hehlmann R, Saussele S, Lauseker M, et al: Randomized comparison of imatinib 400 mg vs. imatinib + IFN vs. imatinib + araC vs. imatinib after IFN vs. imatinib 800 mg: Optimized treatment and survival—Designed first interim analysis of the German CML Study IV. Blood 112:75, 2008 (abstr 184)

**39.** De Lavallade H, Apperley JF, Khorashad J, et al: Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol 26:3358-3363, 2008

**40.** Lucas CM, Austin GM, Knight K, et al: A population study of imatinib in chronic myeloid leukemia demonstrates lower efficacy than in clinical trials. Leukemia 22:1963-1966, 2008

**41.** Kantarjian HM, Larson RA, Guilhot F, et al: Efficacy of imatinib dose escalation in patients with chronic myeloid leukemia in chronic phase. Cancer 115: 551-560, 2009

**42.** Castagnetti F, Palandri F, Amabile M, et al: Results of high-dose imatinib mesylate in intermediate Sokal risk chronic myeloid leukemia patients in early chronic phase: A phase II trial of the Gimema CML WP. Blood 113:3428-3434, 2009

**43.** Jabbour E, Kantarjian HM, Jones D, et al: Imatinib mesylate dose escalation is associated with durable response in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. Blood 113:2154-2160, 2009

**44.** Cortes J, Kantarjian H, Goldberg S, et al: High-dose imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: High rates of rapid cytogenetic and molecular responses. J Clin Oncol 27:4754-4759, 2009

**45.** Hughes T, Branford S, While DL, et al: Impact of early dose intensity on cytogenetic and molecular responses in chronic-phase CML patients receiving 600mg/day of imatinib as initial therapy. Blood 112:3965-3972, 2008

**46.** Guilhot F, Mahon FX, Guilhot J, et al: Randomized comparison of imatinib versus imatinib combination therapies in newly diagnosed chronic myeloid leukaemia (CML) patients in chronic phase (CP): First results of the phase III (SPIRIT) trial from the French CML Group (FI LMC). Blood 112:74, 2008 (abstr 183)

**47.** Cortes J, Baccarani M, Guilhot F, et al: A phase III, randomized, open-label study of 400 mg versus 800 mg of imatinib mesylate (IM) in patients (pts) with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase (CML-CP) using molecular endpoints: 1-year results of TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) study. Blood 112:130-131, 2008 (abstr 325)

**48.** Baccarani M, Rosti G, Castagnetti F, et al: A comparison of imatinib 400 mg and 800 mg daily in the first-line treatment of patients with high risk, Philadelphia-positive, chronic myeloid leukaemia: An European LeukemiaNet Study. Blood 113:4497-4504, 2009

**49.** Palandri F, Iacobucci I, Castagnetti F, et al: Front-line treatment of Philadelphia-positive chronic myeloid leukemia with imatinib and interferon-alfa: 5-year outcome. Haematologica 93:770-774, 2008

**50.** Deenik W, van der Holt B, Verhoef GEG, et al: Dose-finding study of imatinib in combination with intravenous cytarabine: Feasibility in newly diagnosed patients with chronic myeloid leukemia. Blood 111:2581-2588, 2008

**51.** Kantarjian HM, Talpaz M, Giles F, et al: New insights into the pathophysiology of chronic myeloid leukemia and imatinib resistance. Ann Intern Med 145:913-923, 2006

**52.** O'Hare T, Eide CA, Deininger MWN: Bcr-Abl kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. Blood 110:2242-2249, 2007

**53.** Hochhaus A, Erben P, Ernst T, et al: Resistance to targeted therapy in chronic myelogenous leukemia. Semin Hematol 44:S15-S24, 2007 (suppl 1)

**54.** Soverini S, Colarossi S, Gnani A, et al: Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: By the GIMEMA Working Party on Chronic Myeloid Leukemia. Clin Cancer Res 12: 7374-7379 2006

**55.** Jabbour E, Kantarjian H, Jones D, et al: Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate. Leukemia 20:1767-1773, 2006

**56.** Nicolini FE, Corm S, Lê QH, et al: Mutation status and clinical outcome of 89 imatinib mesylate-resistant chronic myelogenous leukemia patients: A retrospective analysis from the French Intergroup of CML. Leukemia 20:1061-1066, 2006

**57.** Soverini S, Baccarani M, Iacobucci I, et al: Resistance to tyrosine kinase inhibitors in Philadelphia chromosome–positive leukemias: Which mutations matter? Clin Leukemia 1:223-228, 2007

**58.** Ernst T, Erben P, Müller MC, et al: Dynamics of BCR-ABL mutated clones prior to hematologic or cytogenetic resistance to imatinib. Haematologica 93:186-192, 2008

**59.** Khorashad JS, de Lavallade H, Apperley JF, et al: Finding of kinase domain mutations in patients with chronic-phase chronic myeloid leukemia responding to imatinib may identify those at high risk of disease progression. J Clin Oncol 26:4806-4813, 2008

**60.** Soverini S, Colarossi S, Gnani A, et al: Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. Haematologica 92:401-403, 2007

**61.** Soverini S, Iacobucci I, Baccarani M, et al: Targeted therapy and the T315I mutation in Philadelphia-positive leukemias. Haematologica 92: 437-439, 2007

**62.** Khorashad JS, Anand M, Marin D, et al: The presence of a BCR-ABL mutant allele in CML does not always explain clinical resistance to imatinib. Leukemia 20:658-663, 2006

**63.** Sherbenou DW, Wong MJ, Humayun A, et al: Mutations of the BCR-ABL-kinase domain occur in a minority of patients with stable complete cytogenetic response to imatinib. Leukemia 21:489-493, 2007

**64.** Jabbour E, Kantarjian HM, Jones D, et al: Characteristics and outcome of chronic myeloid leukemia patients with F317L BCR-ABL kinase domain mutation after therapy with tyrosine kinase inhibitors. Blood 112:4839-4841, 2008

**65.** Jabbour E, Kantarjian H, Jones D, et al: Characteristics and outcomes of patients with chronic myeloid leukemia and T315I mutation following failure of imatinib mesylate therapy. Blood 112:53-55, 2008

**66.** Nicolini FE, Hayette S, Corm S, et al: Clinical outcome of 27 imatinib mesylate–resistant chronic myelogenous leukemia patients harboring a T315I BCR-ABL mutation. Haematologica 92:1238-1241, 2007

**67.** Shah NP, Nicoll JM, Nagar B, et al: Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell 2:117-125, 2002

**68.** Corbin AS, La Rosee P, Stoffregen EP, et al: Several BCR-ABL kinase domain mutants associated with imatinib mesylate resistance remain sensitive to imatinib. Blood 101:4611-4614,2003

**69.** Azam M, Latek RR, Daley GQ: Mechanisms of autoinhibition and STI571/imatinib resistance revealed by mutagenesis of BCR-ABL. Cell 112:831-843, 2003

**70.** O'Hare T, Walters DK, Stoffregen EP, et al: In vitro activity of BCR-ABL inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistance ABL kinase domain mutants. Cancer Res 65:4500-4505, 2005



 

**71.** Manley PW, Cowan-Jacob SW, Mestan J: Advances in the structural biology, design, and clinical development of BCR-ABL kinase inhibitors for the treatment of chronic myeloid leukemia. Biophys Acta 1754:3-13, 2005

**72.** Bradeen HA, Eide CA; O'Hare T, et al: Comparison of imatinib mesylate, dasatinib (BMS-354825), and nilotinib (AMN107) in an N-ethyl-N-nitrosourea (ENU) –based mutagenesis screen: High efficacy of drug combinations. Blood 108:2332-2338, 2006

**73.** Ray A, Cowan-Jacob SW, Manley PW, et al: Indentification of BCR-ABL point mutations conferring resistance to the ABL kinase inhibitor AMN107 (nilotinib) by random mutagenesis study. Blood 109: 5011-5015, 2007

**74.** Redaelli S, Piazza R, Rostagno R, et al: Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol 27:469-471, 2009

**75.** Larson RA, Druker BJ, Guilhot F, et al: Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: A subanalysis of the IRIS study. Blood 111:4022-4028, 2008

**76.** Peng B, Loyd P, Schran H: Clinical pharmacokinetics of imatinib. Clin Pharmacokinet 44:879-894, 2005

**77.** Schmidli H., Peng B, Rivioere G-J, et al: Population pharmacokinetics of imatinib mesylate in patients with chronic phase chronic myeloid leukaemia: Results of a phase III study. Br J Clin Pharmacol 60:35-44, 2005

**78.** Guilhot F, Hughes TP, Cortes J, et al: Imatinib (IM) pharmacokinetics (PK) exposure and its correlation with clinical outcome in patients with chronic-phase chronic myeloid leukemia (CML-CP) for 400 mg and 800 mg daily doses (Tyrosine Kinase Dose Optimization Study [TOPS]). Blood 112:170, 2008 (abstr 447)

**79.** Nicaise C, Wang X, Roy A, et al: Dasatinib pharmacokinetics and exposure-response (E-R): Relationship to efficacy and safety in patients with chronic myelogenous leukemia in chronic phase (CML-CP). Haematologica 93:227, 2008 (abstr 0559)

**80.** Hochhaus A, Kreil S, Corbin AS, et al: Molecular and chromosomal mechanins of resistance to imatinib (STI571) therapy. Leukemia 16:2190-2196, 2002

**81.** Branford S, Rudzki Z, Walsh S, et al: Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. Blood 102:276-283, 2003

**82.** Soverini S, Martinelli G, Amabile M, et al: Denaturing-HPLC–based assay for detection of ABL mutations in chronic myeloid leukemia patients resistant to imatinib. Clin Chem 50:1205-1213, 2004

**83.** Deininger MW, McGreevey L, Willis S, et al: Detection of ABL kinase domain mutations with denaturing high-performance liquid chromatography. Leukemia 18:864-871, 2004

**84.** Willis SG, Lange T, Demehri et al: High-sensitivity detection of BCR-ABL kinase domain mutations in imatinib-naive patients: Correlation with clonal cytogenetic evolution but not response to therapy. Blood 106:2128-2137, 2005

**85.** Cortes J, Jabbour E, Kantarjian H, et al: Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. Blood 110: 4005-4011, 2007

**86.** Soverini S, Gnani A, Colarossi S, et al: Long-term mutation follow-up of Philadelphia chromosome–positive leukemia patients treated with second-generation tyrosine kinase inhibitors after imatinib failure shows that newly acquired BCR-ABL kinase domain mutations leading to relapse are mainly detected during the first year. Blood 112:737-738, 2008 (abstr 2118)

**87.** Rousselot P, Huguet F, Rea D, et al: Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. Blood 109:58-60, 2007

**88.** Mahon FX, Huguet F, Guilhot F, et al: Is it possible to stop imatinib in patients with chronic myeloid leukemia? An update from a French Pilot Study and first results from the multicentre Stop Imatinib (STIM) study. Blood 112:76, 2008 (abstr 187)

**89.** Ross MD, Grigg A, Schwarer, Arthur C, et al: The majority of chronic myeloid leukaemia patients who cease imatinib after achieving a sustained complete molecular response (CMR) remain in CMR, and any relapses occur early. Blood 112:402-403, 2008 (abstr 1102)

**90.** Pye SM, Cortes J, Ault P, et al: The effects of imatinib on pregnancy outcome. Blood 111:5505-5508, 2008

**91.** Goldman JM, Rizzo JD, Jabocinski KA, et al: Long term outcome after allogeneic stem-cell transplantation for CML. Hematol J 5:98, 2004 (abstr 266)

**92.** Gratwohl A, Brand R, Apperley J, et al: Allogeneic hematopoietic stem-cell transplantation for chronic myeloid leukemia in Europe 2006: Transplant activity, long-term data and current results—An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Haematologica 91: 513-521, 2006

**93.** Gratwohl A,Hermans J,Goldman JM, et al: Risk assessment for patients whith chronic myeloid leukaemia before allogeneic blood or marrow transplantation: Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Lancet 352:1087-1092, 1998

**94.** Passweg JR,Walker I,Sobocinski KA, et al: Validation and extension of the EBMT risk score for patients with chronic myeloid leukemia receiving allogeneic haematopoietic stem-cell transplants. Br J Haematol 125:613-620, 2004

**95.** Deininger M, Schleuning M, Greinix H, et al: The effect of prior exposure to imatinib on transplant-related mortality. Haematologica 91:452-459, 2006

**96.** Oehler VG, Gooley T, Snyder DS, et al: The effects of imatinib mesylate treatment before allogeneic tranplantation for chronic myeloid leukemia. Blood 109:1782-1789, 2007

**97.** Lee SJ, Kukreja M, Wang T, et al: Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. Blood 112:3500-3507, 2008

**98.** Jabbour E, Cortes J, Kantarjian H, et al: Novel tyrosine kinase inhibitor therapy before allogeneic stem-cell transplantation in patients with chronic myeloid leukemia. Cancer 110:340-344, 2007

**99.** Shimoni A, Leiba M, Martineau G, et al: Prior treatment with the tyrosine kinase inhibitors dasatinib and nilotinib allows stem-cell transplantation (SCT) in a less advanced disease phase and does not increase SCT toxicity in patients with chronic myelogenous leukemia and Philadelphia-positive acute lymphoblastic leukemia. Leukemia 23:190-194, 2009

**100.** Baccarani M, Rosti G, Saglio G, et al: Dasatinib time to and durability of major and complete cytogenetic response (MCyR and CCyR) in patients with chronic myeloid leukemia in chronic phase (CML-CP). Blood 112:172, 2008 (abstr 450)

**101.** Hochhaus A, Müller M, Radich J, et al: Dasatinib-associated major molecular responses are rapidly achieved in patients with chronic myeloid leukemia in chronic phase (CML-CP) following resistance, suboptimal response, or intolerance on imatinib. Blood. 112:400, 2008 (abstr 1095)

**102.** Hochhaus A, Müller MC, Radich J, et al: Dasatinib-associated major molecular responses in patients with chronic myeloid leukemia in chronic phase following imatinib failure: Response dynamics and predictive value. Leukemia 23:1628-1633, 2009

**103.** Cortes J, O'Brien S, Borthakur G, et al: Efficacy of dasatinib in patients with previously untreated chronic myelogenous leukemia (CML) in early chronic phase (CML-CP). Blood 112:74, 2008 (abstr 182)

**104.** Rosti G, Castagnetti F, Poerio A, et al: High and early rates of cytogenetic and molecular response with nilotinib 800 mg daily as first line treatment of Ph-positive chronic myeloid leukemia in chronic phase: Results of a phase 2 trial of the GIMEMA CML Working Party. Blood 112:73-74, 2008 (abstr 181)

**105.** Cortes J, O'Brien S, Jones D, et al: Efficacy of nilotinib (formely AMN107) in patients with newly diagnosed, previously untreated Philadelphia chromosome (Ph) –positive chronic myelogenous leukemia in early chronic phase (CML-CP). Blood 112:170, 2008 (abstr 446)

**106.** Marin D, Milojkovic D, Olavarria E, et al: European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. Blood 112:4437-4444, 2008

**107.** Kim DHD, Popradi G, Sriharsha L, et al: No significance of derivative chromosome 9 deletion on the clearance kinetics of BCR-ABL fusion transcripts, cytogenetic or molecular response, loss of response, or treatment failure to imatinib mesylate therapy for chronic myeloid leukemia. Cancer 113: 772-781, 2008

**108.** Richebourg S, Eclache V, Perot C, et al: Mechanisms of genesis of variant translocations in chronic myeloid leukemia are not correlated with ABL1 or BCR deletion status or response to imatinib therapy. Cancer Gen Cytogen 182:95-102, 2008

**109.** Batty N, Kantarjian H, Borthakur G, et al: Patients with chronic myeloid leukemia with variant Philadelphia chromosome (Ph) translocations have a similar outcome as those with classic Ph when treated with imatinib or 2nd generation TKI. Blood 112:1108, 2008 (abstr 3228)

**110.** Radich JP, Dai H, Mao M, et al: Gene expression changes associated with progression and response in chronic myeloid leukemia. PNAS 103: 2794-2799, 2006

**111.** Zheng C, Li L, Haak M, et al: Gene expression profiling of CD34+ cells identifies a molecular signature of chronic myeloid leukemia blast crisis. Leukemia 20:1028-1034, 2006

**112.** Villuendas R, Steegmann JL, Pollán M, et al: Identification of genes involved in imatinib resistance in CML: A gene-expression profiling approach. Leukemia 20:1047-1054, 2006

**113.** Frank O, Brors B, Fabarius A, et al: Gene expression signature of primary imatinib-resistance chronic myeloid leukemia patients. Leukemia 20: 1400-1407, 2006

**114.** Chung YJ, Kim TM, Kim DW, et al: Gene expression signatures associated with the resistance to imatinib. Leukemia 20:1542-1550, 2006

**115.** Diaz-Blanco E, Bruns I, Neumann F, et al: Molecular signature of CD34+ hematopoietic stem and progenitor cells of patients with CML in chronic phase. Leukemia 21:494-504, 2007

**116.** Alvarado Y, Kantarjian H, O'Brien S, et al: Significance of suboptimal response to imatinib, as defined by the European LeukemiaNet, in long-term outcome for patients with early chronic-phase chronic myeloid leukemia. Cancer 115:3709-3718, 2009

**117.** Kantarjian H, O'Brien S, Shan J, et al: Cytogenetic and molecular responses and outcome in chronic myelogenous leukemia. Cancer 112:837-845, 2008

**118.** Hughes T, Hochhaus A, Branford S, et al: Reduction of BCR-ABL transcript levels at 6, 12, and 18 months correlates with long-term outcomes on imatinib (IM) at 72 mo: An analysis from the international randomized study of interferon versus STI571 (IRIS) in patients with chronic phase chronic myeloid leukemia (CML-CP). Blood 112:129-130, 2008 (abstr 334)

**119.** Press RD, Love Z, Tronnes AA, et al: BCR-ABL mRNA levels at and after the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib mesylate-treated patients with CML. Blood 107:4250-4256, 2006

**120.** Press RD, Galderisi C, Yang R, et al: A half-log increase in BCR-ABL RNA predicts a higher risk of relapse in patients with chronic myeloid leukemia with an imatinib-induced complete cytogenetic response. Clin Cancer Res 13:6136-6143, 2007

**121.** Müller MC, Hanfstein B, Erben P, et al: Molecular response to first line imatinib therapy is predictive for long-term event-free survival in patients with chronic-phase chronic myelogenous leukaemia: An interim analysis of the randomized German CML study IV. Blood 112:129, 2008 (abstr 333)

**122.** Branford S, Lawrence R, Grigg A, et al: Long-term follow-up of patients with CML in chronic phase treated with first-line imatinib suggests that earlier achievement of a major molecular response leads to greater stability of response. Blood 112: 735-736, 2008 (abstr 2113)

**123.** Branford S, Seymour JF, Grigg A, et al: BCR-ABL messenger RNA levels continue to decline in patients with chronic-phase chronic myeloid leukemia treated with imatinib for more than 5 years and approximately half of all first-line treated patients have stable undetectable BCR-ABL using strict sensitivity criteria. Clin Cancer Res 13:7080-7085, 2007

**124.** Kantarjian HM, Shan J, Jones D, et al: Significance of rising levels of minimal residual disease in patients with Philadelphia chromosome–positive chronic myelogenous leukemia (Ph+ CML) in complete cytogenetic response (CGCR). Blood 112:169-170, 2008 (abstr 445)

**125.** Zaccaria A, Valenti AM, Donti E, et al: Persistence of chromosomal abnormalities additional to the Philadelphia chromosome after Philadelphia chromosome disappearance during imatinib therapy for chronic myeloid leukemia. Haematologica 92: 564-565, 2007

**126.** Jabbour E, Kantarjian HM, Abruzzo LV, et al: Chromosomal abnormalities in Philadelphia chromosome–negative metaphases appearing during imatinib mesylate therapy in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Blood 110:2991-2995, 2007

**127.** Deininger MWN, Cortes J, Paquette R, et al: The prognosis for patients with chronic myeloid leukemia who have clonal cytogenetic abnormalities in Philadelphia chromosome–negative cells. Cancer 110:1509-1519, 2007

**128.** Kovitz C, Kantarjian H, Garcia-Manero G, et al: Myelodysplastic syndromes and acute leukemia developing after imatinib mesylate therapy for chronic myeloid leukemia. Blood 108:2811-2813, 2006

**129.** Abruzzese E, Gozzetti A, Galimberti S, et al: Characterization of Ph-negative abnormal clones emerging during imatinib therapy. Cancer 109:2466-2472, 2007

**130.** Tam CS, Kantarjian H, Garcia-Manero G, et al: Failure to achieve a major cytogenetic response by 12 months defines inadequate response in patients receiving nilotinib or dasatinib as second- or subsequent line therapy for chronic myeloid leukemia. Blood 112:516-517, 2008

**131.** Milojkovic D, Bua M, Apperly JF, et al: Prediction of cytogenetic response to second-generation TKI therapy in CML chronic-phase patients who have failed imatinib therapy and early identification of factors that influence survival. Blood 112:129, 2008 (abstr 332)

**132.** Baccarani M, Pane F, Saglio G: Monitoring treatment of chronic myeloid leukemia. Haematologica 92:161-169, 2008

**133.** Kantarjian H, Scheffer C, Jones D, et al: Monitoring the response and course of chronic myeloid leukemia in the modern era of BCR-ABL tyrosine kinase inhibitors: Practical advice on the use and interpretation of monitoring methods. Blood 111:1774-1779, 2008

**134.** Jabbour E, Cortes JE, Kantarjian HM: Molecular monitoring in chronic myeloid leukemia. Cancer 112:2112-2118, 2008

**135.** Reinhold U, Henning E, Leiblein S, et al: FISH for BCR-ABL on interphases of peripheral blood neutrophils but not of unselected white bone marrow cells in CML patients treated with imatinib. Leukemia 17:1925-1929, 2003

**136.** Raanani P, Ben-Bassat I, Gan S, et al: Assessment of the response to imatinib in chronic myeloid leukemia patients: Comparison between the FISH, multiplex, and RT-PCR methods. Eur J Haematol 73:243-250, 2004

**137.** Testoni N, Marzocchi G, Luatti S, et al: A prospective study in Ph+ chronic myeloid leukemia (CML) patients showing that interphase fluorescence in situ hybridization (I-FISH) is effective as conventional cytogenetics for definition of cytogenetic response to imatinib: Correlation with molecular response (A GIMEMA CML WP study). Blood, 2009, in press

**138.** Hughes T, Deininger M, Hochhaus A, et al: Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: Review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 108:28-37, 2006

**139.** Saldanha J, Silvy M, Beaufils N, et al: Characterization of a reference material for BCR-ABL (M-BCR) mRNA quantitation by real-time amplification assays: Towards new standards for gene expression measurements. Leukemia 21:1481-1487, 2007

**140.** Müller MC, Erben P, Saglio G, et al: Harmonization of a BCR-ABL mRNA quantification using a uniform multifunctional control plasmid in 37 international laboratories. Leukemia 22:96-102, 2008

**141.** Branford S, Fletcher L, Cross NCP, et al: Desirable performance characteristics for BCR-ABL measurement on an international reporting scale to allow consistent interpretation of individual patient response and comparison of response rates between clinical trials. Blood 112:3330-3337, 2008

**142.** Jones D, Kamel-Reid S, Bahler D, et al: Laboratory practice guidelines for detecting and reporting BCR-ABL drug resistance mutations in chronic myelogenous leukemia and acute lymphoblastic leukemia. J Mol Diagn 11:4-11, 2009

**143.** Branford S, Lawrence R, Fletcher L, et al: The initial molecular response of chronic phase CML patients treated with second generation ABL inhibitor therapy after imatinib failure can predict inadequate response and provide indications for rational mutation screening. Blood 112:128, 2008 (abstr 331)



 