EUROPEAN LEUKEMIANET RECOMMENDATIONS FOR THE MANAGEMENT OF CHRONIC MYELOID LEUKEMIA. 2013.

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ABSTRACT

Advances in chronic myeloid leukemia treatment, particularly regarding tyrosine kinase inhibitors (TKIs), mandate regular updating of concepts and management. An ELN expert panel reviewed prior and new studies, to update recommendations made in 2009. We recommend as initial treatment imatinib or nilotinib or dasatinib. Response is assessed with standardized RQ-PCR and/or cytogenetics at 3, 6, and 12 months. BCR-ABL1 transcript levels $\leq 10\%$ at 3 months, $<1\%$ at 6 months, and $\leq 0.1\%$ from 12 months onward, define optimal response, while $>10\%$ at 6 months and $>1\%$ from 12 months onward define failure, mandating a change of treatment. Similarly, partial cytogenetic response (PCyR) at 3 months and complete CyR (CCyR) from 6 months onward define optimal response, while no CyR (Ph+$>95\%$) at 3 months, less than PCyR at 6 months, and less than CCyR from 12 months onward, define failure. Between optimal and failure, there is an intermediate warning zone requiring more frequent monitoring. Similar definitions are provided for response to 2nd line therapy. Specific recommendations are made for patients in accelerated and blastic phase, and for allogeneic stem cell transplantation. Optimal responders should continue therapy indefinitely, with careful surveillance, or can be enrolled in controlled studies of treatment discontinuation, once a deeper molecular response is achieved.
INTRODUCTION

The management of Philadelphia chromosome-positive (Ph+), BCR-ABL1+, chronic myeloid leukemia (CML) has undergone a profound evolution over a relatively short period of time, starting with allogeneic stem cell transplantation (alloSCT), and recombinant interferon-alfa (rIFNα), and more recently, and most significantly, with the tyrosine kinase inhibitors (TKIs).\textsuperscript{1-3} To ensure for a given patient the best possible duration and quality of life, to avoid unnecessary complications, and potentially achieve a cure, physicians and patients also must understand the proper use of available drugs, the significance of disease endpoints, the critical importance of monitoring, and, in some cases, the use of alloSCT as appropriate therapy. The European LeukemiaNet (ELN) had proposed recommendations for the management of CML in 2006 and 2009.\textsuperscript{4,5} This is the third version of these recommendations, based on data gained from new studies as well as from the update of the most relevant previous studies. We discuss and make recommendations about which TKI should be used frontline and secondline, the important endpoints of treatment, the best approach to evaluating and monitoring response, the reporting and interpretation of molecular and cytogenetic tests, the information provided by mutational analysis, the importance of side-effects, and the role of alloSCT.
METHODS

The composition of the ELN panel for recommendations in CML was increased to include thirty-two experts from Europe, America, and the Asian-Pacific areas. The panel met four times, at international meetings of the American Society of Hematology (ASH) 2011 (San Diego), the European Haematology Association (EHA) 2012 (Amsterdam), the European School of Haematology/International CML Foundation 2012 (Baltimore), and ASH 2012 (Atlanta). Before each meeting, a set of questions was submitted to panel members, and the agenda of the meetings was based on a summary and analysis of the answers from all panel members. After four meetings, discordant opinions were harmonized, and consensus was reached for all recommendations. The costs for the meetings, and for the preparation of the interim and final reports, were borne entirely by ELN, a research network of excellence funded by the European Union. There was no financial support from industry for any activity. At the EHA 2012 meeting, representatives of two companies (Novartis Pharma and Bristol-Myers Squibb) were invited to present to the panel an unpublished update of their respective studies, ENESTnd, and DASISION, but were not invited to the discussion of the data. Treatment recommendations are limited to the TKIs that have been approved with at least one indication in CML, either by the US Federal Drug Administration (FDA) or/and by the European Medicine Agency (EMA). These drugs will be listed in order of FDA approval. We acknowledge that not all these drugs may be available worldwide, and that differences in price could make the use of some of these drugs problematic in some countries. The relevant papers that appeared between the publication of the second version of the recommendations in 2009, and February 2013, were identified through the PubMed database and were comprehensively and critically reviewed. With few exceptions, only papers published after 2008 were referenced. The panel also reviewed and utilized as appropriate the abstracts presented at the latest meetings of the EHA (June 2012) and of the ASH (December 2012).
DEFINITIONS

The definitions of chronic phase (CP), accelerated phase (AP), and blastic phase (BP) (Table 1) were unchanged from prior published versions. For treatment-naive, CP patients, three risk scores were analyzed (Table 2), Sokal, Euro, and EUTOS. The definitions of complete hematologic response (CHR) and of cytogenetic responses (CyR), were maintained from prior versions. We agreed that only chromosome banding analysis (CBA) of marrow cell metaphases can be used to assess the degree of CyR, with at least 20 metaphases analysed, and that fluorescence in-situ-hybridization (FISH) of blood interphase cell nuclei could be substituted for CBA of marrow cell metaphases only for the assessment of complete CyR (CCyR), which is then defined by less than 1% BCR-ABL1 positive nuclei out of at least 200 nuclei. Molecular response is best assessed according to the International Scale (IS), as the ratio of BCR-ABL1 transcripts to ABL1 transcripts, or other internationally recognized control transcripts, and it is expressed and reported as BCR-ABL1 %, on a log scale, where 10%, 1%, 0.1%, 0.01%, 0.0032%, and 0.001% correspond to a decrease of 1, 2, 3, 4, 4.5, and 5 logs respectively below the standard baseline that was used in the IRIS study. A BCR-ABL1 expression of 0.1% or less corresponds to major molecular response (MMR). We further confirm that the following criteria should be used to define deep MR14. MR10 = either (i) detectable disease with <0.01% BCR-ABL1 IS or (ii) undetectable disease in cDNA with >10,000 ABL1 transcripts; MR4.5 = either (i) detectable disease with <0.0032% BCR-ABL1 IS or (ii) undetectable disease in cDNA with >32,000 ABL1 transcripts in the same volume of cDNA used to test for BCR-ABL1. Assay sensitivity should be defined in a standardized manner when BCR-ABL1 mRNA is undetectable. The term “complete molecular response” should be avoided, and substituted by the term “molecularly undetectable leukemia”, with specification of the number of the control gene transcript copies. These working definitions depend critically on the ability of testing laboratories to measure absolute numbers of control gene transcripts in a comparable manner, as well as their ability to achieve the PCR sensitivity required for BCR-ABL1 detection.
DATA REVIEW

IMATINIB

Several studies of imatinib firstline have been updated or newly reported (15-39). The proportion of patients who achieved CCyR and MMR after one year of 400 mg daily ranged from 49% to 77%, and from 18% to 58%, respectively\textsuperscript{23,24,26,35-39} (Suppl. Table 1). With 600 or 800 mg daily, the CCyR rate ranged from 63% to 88%, and the MMR rate from 43% to 47% (Suppl. Table 1). A superiority of 800 mg daily was reported in one large randomized study.\textsuperscript{31} In high risk patients,\textsuperscript{15,16,24,26,35-39} the CCyR and the MMR rates at one year ranged from 48% to 64%, and from 16% to 40%, respectively (Suppl. Table 2). The outcome data, with a median follow-up ranging between 3.2 and more than 6 years, are reported in Table 3. At $\geq$5 years, progression-free survival (PFS) ranged between 83% and 94%, and overall survival (OS) ranged between 83% and 97%. The number of patients still on initial imatinib treatment was reported at 63% to 79% after 3 to 5 years, and at about 50% after 8 years.\textsuperscript{11,13,25-31,34} To date, there have been no other reports of more, or of new, clinically relevant, late side-effects, or complications.

IMATINIB COMBINATIONS

Imatinib has been tested in combination with low dose arabinosyl cytosine, without showing superiority,\textsuperscript{28,31} and with IFN$\alpha$,\textsuperscript{28,31,40,41} in CP, newly diagnosed patients. In the French SPIRIT trial, using pegylated rIFN$\alpha$2a, the rates of MMR and MR$^4.0$ were significantly higher for patients treated with the combination of imatinib 400 mg daily and Peg-rIFN$\alpha$2a (90, then 45 $\mu$g weekly) compared to patients treated with imatinib alone: 30% vs. 14% (p=0.001) at one year, and 38% vs. 21% (p=0.001) at 2 years.\textsuperscript{28} In the Nordic and MD Anderson Cancer Center (MDACC) trials, patients were assigned to a combination of imatinib 400 mg daily\textsuperscript{40} or 400 mg twice daily,\textsuperscript{41} and pegylated rIFN-"alpha"2b, 50 $\mu$g\textsuperscript{40} or 0.5 $\mu$g/kg weekly.\textsuperscript{41} In the Nordic study the MMR rate at one year was higher in the combination arm. In the MDACC study, the MMR and the CCyR rates were the same in both arms. In the German CML Study IV, imatinib 400 mg once daily with the non-pegylated form of
rIFNα2a or 2b, 1.5-3.0 MIU three times weekly, was tested vs. imatinib alone; at one and two years, the cumulative incidence of MMR rate was similar to that achieved with imatinib 400 mg and inferior to that with imatinib 800 mg. None of these combination studies has reported a superior PFS or OS.

SECOND GENERATION TKIs, FIRSTLINE

Two prospective, randomized, company-sponsored studies showed an initial superiority of nilotinib and dasatinib over imatinib, used upfront in newly diagnosed patients, particularly in the speed and the depth of the response. The ENESTnd study, testing nilotinib 300 mg twice daily vs. imatinib 400 mg once daily, reported a significantly higher rate of CCyR after 1 and 2 years (80% vs. 65%, and 87% vs. 77%), a significantly higher rate of MMR after 1 year (50% vs. 27%) and 3 years (73% vs. 53%), and a significantly higher rate of MR4.5 after 3 years (32% vs. 15%).35-37 The DASISION study, testing dasatinib 100 mg once daily vs. imatinib 400 mg once daily, reported a significantly higher rate of CCyR after 1 year (83% vs. 72%) but not after 2 years (85% vs. 82%), a significantly higher rate of MMR after 1 year (46% vs. 23%) and 3 years (68% vs. 55%), and a significantly higher rate of MR4.5 after 3 years (22% vs. 12%).38,39 A US and Canadian Intergroup trial of dasatinib vs. imatinib reported similar results.33 The BELA study, testing bosutinib 500 mg once daily vs. imatinib 400 mg once daily, reported a superior MMR rate after 1 year (41% vs. 27%) for the bosutinib arm, but a similar CCyR rate (70% vs. 68%).34 In all four trials, the results of the treatment with 2nd generation TKI were slightly in favor of the new TKIs for the rate of progression or failure, while OS was similar, with a follow-up of three years for nilotinib and dasatinib, and one year for bosutinib. However, only about 70% of the enrolled patients were still on core treatment after 3 years (imatinib, nilotinib, dasatinib),37,39 and after 1 year (imatinib, bosutinib).34
SECOND GENERATION TKIs, SECOND AND THIRD LINE

For several years dasatinib and nilotinib have been approved for second line treatment of CML patients intolerant of or failing imatinib, based on reported CCyR rates of 40% to 60%. Two major, company sponsored, phase 2, single-arm studies, have been updated, reporting an MMR rate of 28% after 2 years (nilotinib) and of 42% after 5 years (dasatinib), stability of the CCyR, once achieved, and PFS of 57% at 4 years with nilotinib and of 56% at 5 years with dasatinib. However, in both studies the proportion of patients who were still on core treatment at 4 to 5 years was only 30% and 31%, respectively.

Bosutinib was approved more recently, for second or subsequent line treatment of CML patients intolerant of or failing imatinib, based on a phase 2, single-arm, company-sponsored study reporting a MCyR rate of 58% and a CCyR rate of 48% in imatinib resistant patients. Ponatinib, a pan-TKI also inhibiting the T315I mutation, has been recently approved for the treatment of the patients who failed previous TKI therapy, based on a company-sponsored, phase 2, single-arm study, reporting that in CP patients resistant to two, and often to three TKIs, ponatinib was able to induce a MCyR, a CCyR, and a MMR in 56%, 46%, and 34% of patients, respectively, with higher rates in patients with a shorter history of disease and treatment, and/or with the T315I mutation. At one year 63% of CP patients were still on core treatment, and about 80% of responders were maintaining the cytogenetic response.

ALLOGENEIC STEM CELL TRANSPLANTATION (alloSCT)

Allogeneic stem cell transplantation (alloSCT) remains the only currently available treatment that can render patients durably molecularly negative but the associated procedural related morbidity and mortality remain a major deterrent. Since our last publication, there have been few new studies in allo-SCT and the interpretation of these is hindered by the lack of information regarding the reason for transplant and the pre- and post-transplant use of TKI. A prospective study was conducted by the German CML Study Group who reported on 84 patients (median age, 37 years)
receiving myeloablative alloSCT between 2003 and 2008, either firstline (n=19) or after imatinib failure (n=37 in CP, n=28 in advanced phases) and with related (36%) or unrelated (64%) donors. OS at 3 years was 88%, 94% and 59% in patients transplanted firstline, after imatinib failure but still in CP, and advanced phase respectively. Transplant related mortality was 8% and chronic graft versus host disease occurred in 46% of patients. The Center for International Blood and Marrow Transplant (CIBMTR) reported retrospectively on 306 patients, aged more than 40 years, who received reduced intensity conditioning or non-myeloablative procedures between 2001 and 2007. Approximately half the patients were in CP at the time of transplant and 74% had received imatinib prior to their graft. In the three age groups 40-49, 50-59 and >60 years, OS, leukemia-free survival, transplant-related mortality and relapse incidence were 54%, 52%, and 41%, 35%, 32%, and 16%, 18%, 20%, and 13%, and 36%, 43%, and 66% respectively. Chronic graft-versus-host disease was reported in about 50% of patients. Pavlu et al updated the Hammersmith results for patients transplanted between 2000 and 2010, with a 6-year OS of 89%, 60% and 30% for patients transplanted with EBMT risk scores of 0-2, 3, and >3 respectively. Outcome for patients transplanted in blast crisis was very poor, with an OS of less than 10%.

**BCR-ABL1 MUTATIONS**

BCR-ABL1 kinase domain point mutations are detectable in about 50% of patients with treatment failure and progression. To date, the clinical impact of mutations has been assessed using low sensitivity techniques (Sanger sequencing). The presence of mutations at lower levels can be identified with more sensitive techniques, such as mass spectrometry or ultra-deep sequencing, but data are not yet sufficient to interpret the clinical relevance of the mutations detected by these more sensitive techniques. Mutations, which should not be confused with ABL1 polymorphisms, are suggestive of genetic instability and of increased risk of progression. More than 80 amino acid substitutions have been reported in association with resistance to imatinib. Dasatinib and nilotinib have much smaller spectra of resistant mutations, but neither inhibit the T315I.
relapsing on nilotinib were most frequently found to have acquired Y253H, E255K/V, F359V/C/I, or T315I mutations, while patients relapsing on dasatinib were most frequently found to have acquired V299L, F317L/V/I/C, T315A, T315I mutations.\textsuperscript{58-63} T315I is also resistant to bosutinib,\textsuperscript{34,68} while ponatinib inhibits T315I in vitro, and is effective in patients with T315 in vivo.\textsuperscript{49-52} Table 4 reports the in vitro sensitivity of the most common $BCR-ABL1$ mutants to imatinib, nilotinib, dasatinib, bosutinib, and ponatinib, expressed as half maximal inhibitory concentration (IC\textsubscript{50}). In CP there is a correlation between the IC\textsubscript{50} value for a specific mutation in vitro and the clinical response in patients harboring the same mutation in vivo, in that patients harboring mutations with higher IC\textsubscript{50} values had lower hematologic and cytogenetic response rates than those harboring mutations with lower IC\textsubscript{50} values; mutations selected in patients developing dasatinib or nilotinib resistance were those with the highest IC\textsubscript{50} values.\textsuperscript{33,34,37,39,43-45,47,48,58-64,69,70}

ADDITIONAL CLONAL CYTOGENETIC ABNORMALITIES EMERGING ON THERAPY

Metaphase karyotyping may reveal additional clonal chromosomal abnormalities in Ph+ cells (CCA/Ph+), a situation referred to as clonal cytogenetic evolution. CCA/Ph+ defines TKI failure. CCA/Ph+ is associated with shorter OS on second-line imatinib (after rIFN failure), but not second-line dasatinib or nilotinib.\textsuperscript{5,76,77} Clonal cytogenetic abnormalities in Ph- cells (CCA/Ph-) occur in 5-10\% of patients and, in the absence of dysplasia, do not seem to adversely affect outcome.\textsuperscript{5,78,79} The exception are abnormalities of chromosome 7 [monosomy 7 and del(7q)], where some case reports indicate a risk of myelodysplasia and acute leukemia, and justify long-term follow-up bone marrow biopsies. Other patients with CCA/Ph- require marrow examination only in case of cytopenias or dysplastic peripheral blood morphology.
BASELINE PROGNOSTIC FACTORS

Several factors have been reported to influence the response to TKI and the outcome. Three prognostic systems, Sokal, Euro, and EUTOS (Table 2), based on simple clinical and hematologic data, have been shown to be still of value. There is no evidence, as yet, that any one of the three risk scores is superior or more convenient, and there is no clear evidence that intermediate risk patients behave differently from low risk ones. Therefore, whichever system is used, we recommend dividing patients into low (including intermediate) and high risk populations.

Chromosome 9 deletions and variant translocations have no value for prognosis whereas CCA/Ph+ have been reported to have an adverse prognostic value, particularly in the case of the so-called “major route” abnormalities, including trisomy 8, trisomy Ph [+der(22)t(9;22)(q34;q11)], isochromosome 17 [i(17)(q10)], trisomy 19, and ider(22)(q10)t(9;22)(q34;q11). High risk and major route CCA/Ph+ can help identify patients eligible for investigational approaches, but in daily practice they do not mandate different initial treatments. Major route CCA/Ph+ developing during treatment were confirmed to be a signal of acceleration.

Many other baseline factors, including the gene expression profiles, specific polymorphisms of genes coding for TKI transmembrane transporters or TKI-mediated apoptosis, as well as the detailed molecular dissection of the genome, have been reported to have prognostic implications, but these data are not yet sufficiently mature to use them for planning treatment.
RESPONSE TO TREATMENT

The response to TKI is the most important prognostic factor. In the previous versions of the ELN recommendations the response to firstline treatment was limited to imatinib. Now that there are more TKIs, we do not recommend which TKI should be used, but which response should be achieved, irrespective of the TKI that is used. The responses are defined as optimal or failure (Table 5). **Optimal** response is associated with the best long-term outcome, that is to say with a duration of life comparable to that of the general population, indicating that there is no indication for a change of that treatment. **Failure** means that the patient should receive a different treatment, to limit the risk of progression and death. Between optimal and failure there is an intermediate zone, that was previously referred to as suboptimal, and is now designated as “warning”. **Warning** implies that the characteristics of the disease and the response to treatment require more frequent monitoring, so as to permit timely changes in therapy, in case of treatment failure.

In the definition of response, a controversial point is the value of early molecular response, particularly after 3 months of treatment. A BCR-ABL1 transcripts level > 10% was reported to be prognostically significant in several studies\(^ {93-103} \). However, the conclusion of the panel is that a single measurement of BCR-ABL transcripts level is not sufficient to define failure necessitating a change of treatment, whereas two tests, at 3 and 6 months, and supplementary tests in between, provide more support for the decision to change the treatment. Failures must be distinguished as either primary (failure to achieve a given response at a given time) or secondary (loss of response) (Table 5).

The definitions of the response to 2\(^{nd}\) line treatment, based on the same concepts, are shown in Table 6. They are limited to dasatinib and nilotinib\(^ {5,42-46,69,77,104-109} \), but until more data become available, they may provisionally serve also for the other TKIs. These definitions have profound therapeutic implications, because they mark the difficult and critical boundaries between TKIs and alloSCT.
TREATMENT RECOMMENDATIONS

It is recommended that in practice, outside of clinical trials, the firstline treatment of CP CML can be any of the three TKIs that have been approved for this indication and are available almost worldwide, namely imatinib (400 mg once daily), nilotinib (300 mg twice daily), and dasatinib (100 mg once daily). These three TKIs can be used also in second or subsequent lines, at the standard, or at a higher dose (400 mg twice daily for imatinib, 400 mg twice daily for nilotinib, and 70 mg twice daily or 140 mg once daily for dasatinib). Bosutinib (500 mg once daily) has been approved by the FDA and EMA for patients resistant or intolerant to prior therapy. Ponatinib (45 mg once daily) has also been approved by FDA for patients resistant or intolerant to prior TKI therapy. Also approved, for patients failing prior TKI therapy, are radotinib, which is available in Korea, and omacetaxine, that is a non-TKI drug approved by the US FDA.

Busulfan is not recommended. Hydroxyurea can be used for a short time before initiating a TKI, until the diagnosis of CML has been confirmed. rIFNα alone is recommended only in the rare circumstances where a TKI cannot be used. The combinations of TKIs and rIFNα are potentially useful, but still investigational. Cytotoxic chemotherapy is never recommended in CP, but may be useful to control BP, and to prepare BP patients for alloSCT.

Treatment recommendations for CP are proposed in Table 7. These recommendations are based on a critical evaluation of efficacy, but it is acknowledged and recommended that the choice of the TKI must take into account tolerability and safety, and also patient characteristics, particularly age and comorbidities which may be predictive of particular toxicities with the different TKIs. In all cases of “warning”, research and investigational studies are warranted, and should be encouraged, to improve treatment results.

AlloSCT will continue to be an important treatment for the-patients who fail to respond durably to TKIs. Over the last 14 years the timing of transplant has changed to 3rd or 4th line after failure of 2nd generation TKIs. However the situation today is more complex given that patients can be treated
upfront with different TKIs. It seems reasonable that for patients in CP, transplant should be reserved for those who are resistant or intolerant to at least one 2\textsuperscript{nd} generation TKI. The nature of conditioning therapy is controversial because in CP there is no evidence at present that myeloablative conditioning offers any advantage over reduced intensity preparative regimens. Patients should be monitored after transplant by RQ-PCR and treated with donor lymphocyte infusion and/or TKI as clinically appropriate. Patients in BP should receive intensive chemotherapy with or without a TKI, with the intention of proceeding to allo-SCT if a second chronic phase can be established. The value of using a TKI as maintenance after allo-SCT is not proven but seems intuitively logical. Transplant conditioning should be myeloabative where possible. Patients in AP should be considered for alloSCT unless they achieve an optimal response with TKIs. Recommendations concerning alloSCT and the timing of donor identification are included in Table 7.

Treatment recommendations for AP and BP are presented in Table 8. They are based on results of single-arm, retrospective and prospective studies,\textsuperscript{4,5,42,114-122} and on panel members experience.\textsuperscript{123,124}
TREATMENT DISCONTINUATION, PREGNANCY

Currently, we recommend that a patient with CML who is responding optimally to treatment continues indefinitely, at the standard recommended dose. There have been controlled attempts to discontinue imatinib in some patients who were in sustained, deep, molecular response (MR4.5 or better).126-129 Approximately 40% of them maintained the same degree of response, with a follow-up of one to four years. Almost all those who had a molecular recurrence achieved again the same level of deep response when treatment with imatinib is resumed. These data provide a proof-of-principle for the hypothesis that TKI treatment can be discontinued safely, even though some BCR-ABL1+ cells always remain detectable.130-132 However the data are still insufficient to make recommendations on discontinuing treatment outside of well designed, prospective, controlled studies. One such study (EUROSKI), sponsored by the ELN, is in progress.133 Alternatives to discontinuation, like the intermittent administration of imatinib, are currently being investigated,134 but should not be undertaken outside of clinical trials. Treatment discontinuation may be considered in individual patients, also outside studies, if proper, high quality, and certified monitoring can be assured at monthly intervals. This is particularly relevant to fertile women who may have achieved an optimal response, because conception and pregnancy are contraindicated during TKI treatment. In these patients, when the optimal response is stable for at least two years, TKI discontinuation with or without the use of rIFNα, can be considered, after informed consent and with very frequent molecular monitoring.
MONITORING

Monitoring can be performed using either a molecular or cytogenetic test, or both, (Table 9) depending on local facilities and on the degree of molecular standardization of the local laboratory.4,5,42,135

Molecular testing must be performed by RQ-PCR on buffy-coat of more than 10 ml of blood, to measure BCR-ABL1 transcripts level, that is expressed as BCR-ABL1 % on the IS11. RQ-PCR should be performed every three months until a MMR (MR3.0 or better) is achieved, then every three to six months. It is not possible to assess achievement of MMR if the IS is not available. However, if transcripts are not detectable with a threshold sensitivity of 10^-4, this is likely in the range of MMR or below. It is important to realize that it is not unusual for PCR results to fluctuate up and down over time, in part because of laboratory technical reasons. If transcript levels have increased >5 times in a single follow-up sample and MMR was lost, the test should be repeated in a shorter time interval, and patients should be questioned carefully about compliance.

If cytogenetics is used, it must be performed by CBA of marrow cell metaphases, counting at least 20 metaphases, at 3, 6, 12 months, until a CCyR is achieved, then every 12 months. CBA can be substituted by FISH on blood cells only when a CCyR has been achieved.

In case of warning, it is recommended to repeat all tests, cytogenetic and molecular, more frequently, even monthly.

In case of treatment failure, or of progression to AP or BP, cytogenetics of marrow cell metaphases, PCR, and mutational analysis should be performed.

If dysplastic morphology or other indications of myelodysplasia develops, such as unexplained or prolonged cytopenia, histopathologic and cytogenetic studies of bone marrow are recommended. Clonal chromosome abnormalities in Ph- cells, which may develop in up to 10% of responders, are a warning only in case of chromosome 7 involvement.
SIDE EFFECTS

The TKIs have different patterns of side-effects, and this should be considered when choosing amongst these drugs. Side effects can be divided into three general categories. The first includes major, grade 3/4, side effects that typically occur during the first phase of treatment, are manageable, but require temporary treatment discontinuation and dose reduction, and can lead to treatment discontinuation in about 10% of patients. The second category includes minor, grade 1/2, side effects that begin early during treatment and can persist for ever, becoming chronic. They are also manageable, and tolerable, in principle, but affect negatively the quality of life, and are a cause of decreased compliance, that is a major cause of failure. Many of these side effects are common to all TKIs, with some differences in frequency and severity, so that several patients can benefit from changing the TKI. The third category includes late, so-called “off-target” complications, that can affect the cardiovascular system, heart and blood vessels, the respiratory system, liver, pancreas, the immune defense, second malignancies, calcium, glucose and lipid metabolism, etc. All TKIs can be toxic to the heart and should be used with great caution in patients with heart failure. Nilotinib has been reported to be associated particularly with arterial pathology, peripheral and coronary. Dasatinib has been reported to be associated particularly with pleura and lung complications. Data on bosutinib and ponatinib are scanty. Overall, the longterm, so called late or off-target complications of second generation TKIs are not yet fully understood and evaluable. Since they are a potential cause of morbidity and mortality, continued clinical monitoring of all patients is required.
DISCUSSION

These recommendations are based primarily on the antileukemic efficacy of TKIs, but it should not be overlooked that the choice of the treatment depends also on other important variables, which affect the quality of life and life itself, including side effects, serious adverse events, and late “off-target” complications. The evaluation of therapeutic efficacy must be based on the clinical outcomes (PFS and OS), but since the data of clinical outcomes require a long observation time, the evaluation is influenced by the so-called early surrogate markers, namely the molecular and the cytogenetic response. However, as it was already pointed-out elsewhere, \(^{160,161}\) survival data should also be interpreted carefully, because different definitions of progression and failure were used in different studies, and even deaths were counted in different ways, whether they had occurred during the so-called core study treatment, or at any time, or whether they were regarded as “related” or “unrelated” to CML.\(^{15-18,21,24,26,28,29,31,35-39}\)

The definition of response has an important operational value, since it is the basis of continuing or changing the treatment. Two points are particularly controversial. One point is the choice of the first TKI.\(^{162-164}\) Two trials have shown an initial superiority of 2\(^{nd}\) generation TKIs vs. imatinib, with significant differences in response, but not yet in outcome.\(^{9-13}\) They justify placing nilotinib and dasatinib in the frontline setting, but do not justify the exclusion of imatinib. The second point is the prognostic value of the depth of molecular response at three months. Many studies, with imatinib, nilotinib, dasatinib, and bosutinib, firstline and secondline, reported that the 10\(^{th}\) BCR-ABL1 transcripts level was prognostically significant.\(^{93-103}\) Therefore, why should 10\(^{th}\) or more BCR-ABL1 transcripts at three months not be considered as treatment failure, leading to a recommendation to change therapy? The conclusion of the panel was mainly based on the recognition that there are no studies showing that the outcome of such patients would be improved, and if so how much, if therapy was changed at 3 months. It should also be noticed that in all but one of the studies, the difference in OS and PFS, though significant, was of the magnitude of about 10\(^{th}\) (survival was about 95\(^{th}\) in case of BCR-ABL1 less than 10\(^{th}\) vs. about 85\(^{th}\) in case of more than
10%), making it problematic to recommend switching all patients to benefit a minority. Also, it should be considered that all the data that support the prognostic value of the 10% cut-off value at 3 months were derived from retrospective analyses of subgroups that had not been predefined in the original study protocols, and that the molecular assays were performed in one or few reference laboratories that may not yet represent the typical standard of molecular testing, worldwide. Therefore, the panel has considered that a single molecular test cannot be sufficient to take such an important decision as the change of treatment. Two tests, at 3 and 6 months, and even better a supplementary test between 3 and 6 months, as it is recommended in case of “warning”, provide a sounder basis for treatment decisions. The issue of very early change is still investigational. The patients not achieving less than 10% after 6 months of therapy are more clearly in need of a change of therapy.

Efficacy is important, but treatment choice does not depend only on efficacy. The introduction of imatinib was celebrated as the beginning of a new era of cancer treatment, in which therapy was, at long last, non toxic, safe, and well tolerated. After more than 10 years these promises were largely fulfilled, because the side effects of imatinib are usually mild, with only rare severe, life-threatening complications. The side-effects of 2nd generation TKIs are somewhat different from those of imatinib, but overall the tolerability profile is comparable. However, the sensitivity and tolerance of patients is changing, not only because of the chronicity of the treatment, but also because the availability of other TKIs makes changes possible, and easier. Even low grade side effects affect quality of life and compliance, and they can justify a change of drug even though there is a therapeutic response.

The problems of late, so-called “off-target”, complications, are more difficult to evaluate and manage, because the information is still inadequate and the follow-up is still short, particularly for 2nd generation TKIs. If the phase of the disease is advanced and the major threat is the disease itself, these considerations may have less value, but for patients in CP, where a normal duration of life is the goal, these considerations are very important, compete with efficacy data, and may deserve
priority. The adaptation of the treatment to the clinical conditions, a careful attention to the health state of the patients, and the timely report of any severe complication, are recommended. The ELN panel has appointed a committee for a detailed and careful analysis and discussion of the side-effects of TKIs that will be the subject of a separate report.

The quality of life is also affected by the very fact that living together with a potentially fatal disease – CML is a cancer, after all – has emotional and social consequences affecting family and career planning, and is accompanied by a variable level of uncertainty and fear. It was not surprising that both physical and mental health were reported to be better and closer to normal in the older than in the younger patients, since the youngers have more and different expectations, not only of a normal life, but also of a life free from leukemia and from treatment. Currently, the major goal of therapy is survival, but it is acknowledged that living without treatment and without detectable leukemia will be a major issue for clinical investigation, requiring the achievement of a deeper molecular response. These findings underscore the importance of age.

The problem of children and adolescents, and also of young adults, is of particular concern. It is believed and recommended that children must be managed and treated like adults, but specific data are limited, and more information pertaining to these particular age groups is necessary. The current cost of TKIs is high, particularly because therapy needs to be continued lifelong. Depending on the country, costs are determined through negotiations among several partners, so that the cost of the same drug can vary from one country to another. In many countries the costs are not completely reimbursable, or some TKIs are not even available. The ELN expert panel has appointed a committee to study and to report soon on the pharmacoeconomic and ethical implications of the treatment of CML, because it is now time to draw attention to the problem and to call for a public debate.
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95. Branford S, Kim DW, Soverini S, et al. Initial molecular response at 3 months may predict both responses and event-free survival at 24 months in imatinib-resistant or -intolerant patients with


Table 1

### Accelerated Phase

<table>
<thead>
<tr>
<th>ELN criteria</th>
<th>WHO criteria</th>
<th>Blast Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Blasts in blood or marrow 15-29%, or blasts plus promyelocytes in blood or marrow more than 30%, with blasts &lt; 30%</td>
<td>- Blasts in blood or marrow 10-19%</td>
<td>- Blasts in blood or marrow  ≥ 30%</td>
</tr>
<tr>
<td>- Basophils in blood ≥ 20%</td>
<td>- Basophils in blood ≥ 20%</td>
<td>- Extramedullary blast proliferation, apart from spleen</td>
</tr>
<tr>
<td>- Persistent thrombocytopenia (&lt; 100 x 10^9/L) unrelated to therapy</td>
<td>- Persistent thrombocytopenia (&lt; 100 x 10^9/L) unrelated to therapy</td>
<td>- Extramedullary blast proliferation, apart from spleen</td>
</tr>
<tr>
<td>- Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), major route, on treatment</td>
<td>- CCA/Ph+ on treatment</td>
<td>- Large foci or clusters of blasts in the bone marrow biopsy</td>
</tr>
</tbody>
</table>

List of the criteria for the definition of accelerated phase (AP) and blast phase (BP), as recommended by ELN⁴,⁵ and by the WHO.⁶ The ELN criteria are those that were used in all main studies of TKI. The use of TKI may require a change of the boundaries between CP, AP and BP and modify to some extent the classic subdivision of CML in three phases, but the data are not yet sufficient for a revision. CCA/Ph+ = Clonal Chromosome Abnormalities in Ph+ cells
<table>
<thead>
<tr>
<th>Study</th>
<th>Calculation</th>
<th>Risk Definition by Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokal et al, 1984&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Exp 0.0116 × (age in years − 43.4) + 0.0345 × (spleen − 7.51) + 0.188 × [(platelet count ÷ 700)&lt;sup&gt;2&lt;/sup&gt; − 0.563] + 0.0887 × (blast cells − 2.10)</td>
<td>low risk, &lt; 0.8 intermediate risk, 0.8-1.2 high risk, &gt; 1.2</td>
</tr>
<tr>
<td>Euro Hasford et al, 1998&lt;sup&gt;8&lt;/sup&gt;</td>
<td>0.666 when age ≥ 50 years + (0.042 × spleen) + 1.0956 when platelet count ≥ 1,500 × 10&lt;sup&gt;9&lt;/sup&gt;L + (0.0584 × blast cells) + 0.20399 when basophils &gt; 3% + (0.0413 × eosinophils) × 100</td>
<td>low risk, ≤ 780 intermediate risk, 781-1,480 high risk, &gt; 1,480</td>
</tr>
<tr>
<td>EUTOS Hasford et al 2011&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Spleen x 4 + basophils x 7</td>
<td>low risk ≤ 87; high risk &gt; 87</td>
</tr>
</tbody>
</table>

**Calculation of relative risk.**

Age is in years. Spleen is in centimeters below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percent of peripheral blood differential. All values must be collected prior to any treatment. To calculate Sokal and Euro risk score: [http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html](http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html). To calculate EUTOS risk score: [http://www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html](http://www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html).
Table 3

Outcomes of patients treated first-line with imatinib.

<table>
<thead>
<tr>
<th>STUDY / SOURCE</th>
<th>Imatinib dose, mg</th>
<th>N° of pts</th>
<th>High risk pts (Sokal / Euro)</th>
<th>OS</th>
<th>PFS</th>
<th>EFS</th>
<th>AT</th>
<th>Follow Up, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS(^{18,19})</td>
<td>400</td>
<td>553</td>
<td>18% (S)</td>
<td>85%</td>
<td>92%</td>
<td>NR</td>
<td>8 years</td>
<td>6 (minimum)</td>
</tr>
<tr>
<td>HAMMERSMITH(^{21,22})</td>
<td>400</td>
<td>204</td>
<td>29% (S)</td>
<td>83%</td>
<td>83%</td>
<td>63%</td>
<td>5 years</td>
<td>3.2 (median)</td>
</tr>
<tr>
<td>HOUSTON(^{28})</td>
<td>400 (19%) / 800 (81%)</td>
<td>258</td>
<td>8% (S)</td>
<td>97%</td>
<td>92%</td>
<td>NR</td>
<td>5 years</td>
<td>4.4 (median)</td>
</tr>
<tr>
<td>PETHEMA(^{27})</td>
<td>400</td>
<td>210</td>
<td>16% (S)</td>
<td>97%</td>
<td>94%</td>
<td>71%</td>
<td>5 years</td>
<td>4.2 (median)</td>
</tr>
<tr>
<td>CZECH REGISTRY(^{30})</td>
<td>400</td>
<td>343</td>
<td>22% (S)</td>
<td>88%</td>
<td>90%</td>
<td>NR</td>
<td>5 years</td>
<td>3.8 (median)</td>
</tr>
<tr>
<td>FRENCH SPIRIT (^{28})</td>
<td>400 (50%) / 600 (50%)</td>
<td>319</td>
<td>24% (S)</td>
<td>NR</td>
<td>92%</td>
<td>NR</td>
<td>5 years</td>
<td>NR</td>
</tr>
<tr>
<td>GIMEMA(^{29})</td>
<td>400 (76%) / 800 (24%)</td>
<td>559</td>
<td>22% (S)</td>
<td>90%</td>
<td>87%</td>
<td>65%</td>
<td>5 years</td>
<td>5.0 (median)</td>
</tr>
<tr>
<td>GERMAN CML STUDY IV(^{31})</td>
<td>*</td>
<td>1551</td>
<td>12% (E)</td>
<td>88%</td>
<td>86%</td>
<td>NR</td>
<td>6 years</td>
<td>5.6 (median)</td>
</tr>
<tr>
<td>SEOUL, St. Mary Hospital(^{32})</td>
<td>400 (83%) / 6-800 (17%)</td>
<td>363</td>
<td>22% (S)</td>
<td>94%</td>
<td>88%</td>
<td>NR</td>
<td>7 years</td>
<td>5.3 (median)</td>
</tr>
</tbody>
</table>

NR = Not Reported

\(^*\)imatinib 400 + IFNα (28%), imatinib 800 (27%), imatinib 400 (26%), imatinib 400 + low dose arabinosyl cytosine (10%), imatinib 400 after IFNα (8%); min = minimum; med = median.

OS = overall survival. PFS = Survival free from progression to AP or BP. EFS = event free survival, where events are death, progression to AP or BP, failure, and treatment discontinuation for any reason, whichever comes first.
<table>
<thead>
<tr>
<th>BCR-ABL1</th>
<th>IMATINIB IC₅₀, range (nM)</th>
<th>NILOTINIB IC₅₀, range (nM)</th>
<th>DASATINIB IC₅₀, range (nM)</th>
<th>BOSUTINIB IC₅₀ (nM)</th>
<th>PONATINIB IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmutated</td>
<td>260 - 678</td>
<td>&lt;10 - 25</td>
<td>0.8 - 1.8</td>
<td>41.6</td>
<td>0.5</td>
</tr>
<tr>
<td>M244V*</td>
<td>1,600 - 3,100</td>
<td>38 - 39</td>
<td>1.3</td>
<td>147.4</td>
<td>2.2</td>
</tr>
<tr>
<td>L248V</td>
<td>1,866 - 10,000</td>
<td>49.5 - 919</td>
<td>9.4</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>G250E*</td>
<td>1,350 - &gt;20,000</td>
<td>48 - 219</td>
<td>1.8 - 8.1</td>
<td>179.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Q252H</td>
<td>734 - 3,120</td>
<td>16 - 70</td>
<td>3.4 - 5.6</td>
<td>33.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Y253F</td>
<td>&gt;6,400 - 8,953</td>
<td>182 - 725</td>
<td>6.3 - 11</td>
<td>40</td>
<td>2.8</td>
</tr>
<tr>
<td>Y253H*</td>
<td>&gt;6,400 - 17,700</td>
<td>450 - 1,300</td>
<td>1.3 - 10</td>
<td>N.A.</td>
<td>6.2</td>
</tr>
<tr>
<td>E255K*</td>
<td>3,174 - 12,100</td>
<td>118 - 566</td>
<td>5.6 - 13</td>
<td>394</td>
<td>14</td>
</tr>
<tr>
<td>E255V</td>
<td>6,111 - 8,953</td>
<td>430 - 725</td>
<td>6.3 - 11</td>
<td>230.1</td>
<td>36</td>
</tr>
<tr>
<td>D276G</td>
<td>1,147</td>
<td>35.3</td>
<td>2.6</td>
<td>25</td>
<td>N.A.</td>
</tr>
<tr>
<td>E279K</td>
<td>1,872</td>
<td>36.5 - 75</td>
<td>3</td>
<td>39.7</td>
<td>N.A.</td>
</tr>
<tr>
<td>V299L</td>
<td>540 - 814</td>
<td>23.7</td>
<td>15.8 - 18</td>
<td>1,086</td>
<td>N.A.</td>
</tr>
<tr>
<td>F311L</td>
<td>480 - 1,300</td>
<td>23</td>
<td>1.3</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>T315I*</td>
<td>&gt;6,400 - &gt;20,000</td>
<td>697 - &gt;10,000</td>
<td>137 - &gt;1,000</td>
<td>1,890</td>
<td>11</td>
</tr>
<tr>
<td>T315A</td>
<td>125</td>
<td>N.A.</td>
<td>760</td>
<td>N.A.</td>
<td>1.6</td>
</tr>
<tr>
<td>F317L*</td>
<td>810 - 7,500</td>
<td>39.2 - 91</td>
<td>7.4 - 18</td>
<td>100.7</td>
<td>1.1</td>
</tr>
<tr>
<td>F317V</td>
<td>500</td>
<td>350</td>
<td>N.A.</td>
<td>N.A.</td>
<td>10</td>
</tr>
<tr>
<td>M351T*</td>
<td>880 - 4,900</td>
<td>7.8 - 38</td>
<td>1.1 - 1.6</td>
<td>29.1</td>
<td>1.5</td>
</tr>
<tr>
<td>F359V*</td>
<td>1,400 - 1,825</td>
<td>91 - 175</td>
<td>2.2 - 2.7</td>
<td>38.6</td>
<td>10</td>
</tr>
<tr>
<td>V379I</td>
<td>1,000 - 1,630</td>
<td>51</td>
<td>0.8</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>L384M*</td>
<td>674 - 2,800</td>
<td>39 - 41.2</td>
<td>4</td>
<td>19.5</td>
<td>N.A.</td>
</tr>
<tr>
<td>L387M</td>
<td>1,000 - 1,100</td>
<td>49</td>
<td>2</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>H396R*</td>
<td>1,750 - 5,400</td>
<td>41 - 55</td>
<td>1.3 - 3</td>
<td>33.7</td>
<td>N.A.</td>
</tr>
<tr>
<td>H396P</td>
<td>850 - 4,300</td>
<td>41 - 43</td>
<td>0.6 - 2</td>
<td>18.1</td>
<td>1.1</td>
</tr>
<tr>
<td>F486S</td>
<td>2,728 – 9,100</td>
<td>32.8 - 87</td>
<td>5.6</td>
<td>96.1</td>
<td>N.A.</td>
</tr>
<tr>
<td>Plasma drug concentration:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmin</td>
<td>2,062 ± 1.334</td>
<td>1,923 ± 1.233</td>
<td>5.5 ± 1.4</td>
<td>268 (30 -1,533)</td>
<td>64.3 ± 29.2</td>
</tr>
<tr>
<td>Cmax</td>
<td>4,402 ± 1.272</td>
<td>2,329 ± 772</td>
<td>133 ± 73.9</td>
<td>392 (80-1,858)</td>
<td>145.4 ± 72.6</td>
</tr>
</tbody>
</table>
In vitro sensitivity of unmutated *BCR/ABL1* and of some more frequent *BCR/ABL1* kinase domain mutants to imatinib, nilotinib, dasatinib, bosutinib, and ponatinib.

The half maximal inhibitory concentration (IC$_{50}$) shown here is universally regarded as a measure of the degree of sensitivity of a *BCR-ABL1* mutant to a given TKI and is experimentally determined by quantifying the TKI concentration required to reduce by 50% viability of a Ba/F3 mouse lymphoblastoid cell line engineered to express that mutant form of *BCR-ABL1*. The table lists all the *BCR-ABL1* mutants for which the IC$_{50}$ values of at least two TKIs are available. For imatinib, dasatinib and nilotinib, ranges of IC$_{50}$ values were provided when differences in IC$_{50}$ values reported by different studies were observed (reviewed in$^5$). For bosutinib and ponatinib, IC$_{50}$ values come from a single study each.$^{68,71}$ The asterisks highlight the ten most frequent mutations.$^{56,59}$ Plasma drug concentration is also given in nM. Values of plasma drug concentration are mean ± standard deviation for imatinib (400 mg once daily), nilotinib (300 mg twice daily), dasatinib (100 mg once daily) and ponatinib (45 mg once daily), and median (range) for bosutinib.$^{34,50,72-75}$ Abbreviations: NA, not available.
### Table 5

<table>
<thead>
<tr>
<th>Time</th>
<th>Optimal Conditions</th>
<th>Warning Conditions</th>
<th>Failure Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>NA</td>
<td>- High risk, or</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CCA/Ph+, major route</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>BCR-ABL1 ≤ 10% and/or Ph+ ≤ 35%</td>
<td>BCR-ABL1 &gt; 10%, and/or Ph+ 36-95%</td>
<td>Non CHR, and/or Ph+ &gt; 95%</td>
</tr>
<tr>
<td>6 months</td>
<td>BCR-ABL1 &lt; 1% and/or Ph + 0</td>
<td>BCR-ABL1 1-10%, and/or Ph + 1-35%</td>
<td>BCR-ABL1 &gt; 10%, and/or Ph + &gt; 35%</td>
</tr>
<tr>
<td>12 months</td>
<td>BCR-ABL1 ≤ 0.1%</td>
<td>BCR-ABL1 0.1-1 %</td>
<td>BCR-ABL1 &gt; 1%, and/or Ph + &gt; 0</td>
</tr>
<tr>
<td>Then, and at any time</td>
<td>BCR-ABL1 ≤ 0.1%</td>
<td>CCA/Ph- (-7, or 7q)</td>
<td>Loss of CHR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Loss of CCyR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Confirmed loss of MMR*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mutations CCA/Ph +</td>
</tr>
</tbody>
</table>

- In two consecutive tests, of which one with a BCR-ABL1 transcripts level ≥ 1%. NA = Not Applicable. MMR = BCR-ABL1 ≤ 0.1% = MR3.0 or better. CCA/Ph+ = Clonal Chromosome Abnormalities in Ph+ cells. CCA/Ph- = Clonal Chromosome Abnormalities in Ph- cells

**Definition of the response to TKIs (any TKI), frontline.** The definitions are the same for patients in CP, AP, and BP, and apply also to second line treatment, when frontline treatment was changed for intolerance. The response can be assessed either with a molecular or a cytogenetic test, but both are recommended whenever possible. Cut-off values have been used to define the boundaries between optimal and warning, and between warning and failures. Since cut-off values are subjected to fluctuations, in case of cytogenetic or molecular data close to the indicated values, a repetition of the tests is recommended. After 12 months, if an MMR is achieved, the response can be assessed by RQ-PCR every 3 to 6 months, and cytogenetics is required only in case of failure or if standardized molecular testing is not available. Notice that MMR (MR3.0 or better) is optimal for survival, but that a deeper response is likely to be required for a successful discontinuation of treatment.
### Table 6

<table>
<thead>
<tr>
<th>Time</th>
<th>OPTIMAL</th>
<th>WARNING</th>
<th>FAILURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>NA</td>
<td>No CHR or loss of CHR on imatinib, or Lack to CyR to 1st line TKI, or High risk</td>
<td>NA</td>
</tr>
<tr>
<td>3 months</td>
<td>BCR-ABL1 ≤ 10%, and/or Ph+ &lt; 65%</td>
<td>BCR-ABL1 &gt; 10%, and/or Ph+ 65-95%</td>
<td>No CHR, or Ph+ &gt; 95%, or New mutations</td>
</tr>
<tr>
<td>6 months</td>
<td>BCR-ABL1 ≤ 10%, and/or Ph+ &lt; 35%</td>
<td>Ph+ 35-65%</td>
<td>BCR-ABL1 &gt; 10%, and/or Ph+ &gt; 65%, and/or New mutations</td>
</tr>
<tr>
<td>12 months</td>
<td>BCR-ABL1 &lt; 1%, and/or Ph + 0</td>
<td>BCR-ABL1 1-10% and/or Ph + 1-35%</td>
<td>BCR-ABL1 &gt; 10%, and/or Ph + &gt; 35%, and/or New mutations</td>
</tr>
<tr>
<td>Then, and at any time</td>
<td>BCR-ABL1 ≤ 0.1%</td>
<td>CCA/Ph- (-7 or 7q-) or BCR-ABL1 &gt; 0.1%</td>
<td>Loss of CHR, or Loss of CCyR or PCyR New mutations Confirmed loss of MMR</td>
</tr>
</tbody>
</table>

* In two consecutive tests, of which one with a BCR-ABL transcripts level ≥ 1%. NA = Not Applicable. CCA/Ph+ = Clonal Chromosome Abnormalities in Ph+ cells. CCA/Ph- = Clonal Chromosome Abnormalities in Ph- cells

**Definitions of the response to 2nd line therapy, in case of failure of imatinib.** These definitions are mainly based on data reported for nilotinib and dasatinib, but can be used provisionally also for bosutinib and ponatinib, until more data will be available. These definitions cannot apply to the evaluation of the response to 3rd line treatment.
**Table 7**

<table>
<thead>
<tr>
<th>Line</th>
<th>Scenario</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>Imatinib, or nilotinib, or Dasatinib</td>
<td>HLA type patients and sibs only in case of baseline warnings (high risk, major route CCA/Ph+)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line, intolerance to the first TKI</td>
<td>Anyone of the other TKIs approved firstline (imatinib, nilotinib, dasatinib)</td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line, failure of imatinib firstline</td>
<td>Dasatinib, or nilotinib, or bosutinib, or ponatinib.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA type patients and sibs.</td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line, failure of nilotinib firstline</td>
<td>Dasatinib, or bosutinib, or ponatinib.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA type patients and sibs. Search for an unrelated stem cell donor. Consider alloSCT</td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line, failure of dasatinib firstline</td>
<td>Nilotinib, or bosutinib, or ponatinib.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA type patients and sibs. Search for an unrelated stem cell donor. Consider alloSCT</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line, failure of, or/and intolerance to, two TKIs</td>
<td>Anyone of the remaining TKIs. AlloSCT recommended in all eligible patients</td>
<td></td>
</tr>
<tr>
<td>Any line, T315I mutation</td>
<td>Ponatinib.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA type patients and sibs. Search for an unrelated stem cell donor. Consider alloSCT</td>
<td></td>
</tr>
</tbody>
</table>
Chronic phase, treatment recommendations for 1st, 2nd and subsequent lines of treatment. In firstline, the choice is among three TKIs that are currently approved, available, but not always reimbursable, worldwide. The respective, approved doses are 400 mg once daily for imatinib, 300 mg twice daily for nilotinib, and 100 mg one daily for dasatinib. Higher doses of all three drugs were tested, and a superiority of a higher dose was reported only in one study of imatinib. There are no recognized and solid criteria that can be recommended for making the choice. Provisional clinical criteria can be the characteristics of the disease (high risk, CCA/Ph+) on one hand, and the relationship between the patient (comorbidities) and the safety profile of the drugs on the other hand. In second line, a change of drug is preferred to an increase of imatinib dose. The switch from one TKI to another must always take into account the presence and type of a mutation (see Table 4), the side-effects and the toxicity of the previous TKI, and different comorbidities that can be of concern with different TKIs. The definition of intolerance may be sometimes objective and based on evidence, but sometimes is subjective and open to criticism. Experience and common sense suggest that a patient who is intolerant to one TKI can easily respond to other TKIs, while a patient who has failed one TKI and is intolerant to another TKI, is at considerable risk of failure. Recommendations for alloSCT are based on the results from HLA-identical sibs or HLA-matched unrelated donors, myeloablative and RIC, T-cell replete or T-cell depleted. They do not include cord blood or haplotype matched donors, or experimental conditioning regimens. The EBMT risk score is still of value, although insufficient numbers of patients have been transplanted in recent years and after TKIs therapy to allow a robust re-analysis.
### Table 8

| AP and BP, in newly diagnosed, TKI naïve patients: | Imatinib 400 mg twice daily, or dasatinib 70 mg twice daily or 140 mg once daily. Stem cell donor search. Then, alloSCT is recommended for all BP patients and for the AP patients who do not achieve an optimal response. Chemotherapy may be required before alloSCT, to control the disease. |

| AP and BP, as a progression from CP, in TKI pretreated patients: | Anyone of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then alloSCT in all patients. Chemotherapy is frequently required to make patients eligible to alloSCT. |

### Treatment strategy recommendations for CML in AP or BP.

In patients treatment naïve, AP is believed to be close to high risk CP, so that TKIs have priority. In patients who progress to AP or BP during TKI therapy, the response to any subsequent treatment is poorer, and less durable, so that alloSCT is recommended for all the patients who are eligible to the procedure. However, in these patients, not only TKIs but also cytotoxic chemotherapy may be necessary to reinsert some degree of remission to permit alloSCT. In case of uncontrolled, resistant, BP, alloSCT is not recommended. All recommendations to alloSCT implies that the patient is eligible for that procedure. Notice that nilotinib was tested, but was not approved, for the treatment of BP.\textsuperscript{119,121,122}
Table 9

| At diagnosis | - Chromosome banding analysis (CBA) of marrow cell metaphases,  
|             | - FISH in case of Ph negativity, to identify variant, cryptic translocations,  
|             | - Qualitative PCR (identification of transcript type). |

| During treatment | - Quantitative, real-time PCR (RQ-PCR) for the determination of BCR/ABL1 transcripts level on the international scale, to be performed every 3 months until a MMR (BCR-ABL ≤ 0.15, or MR^{3.0}) has been achieved, then every 3 to 6 months,  
|                 | and / or  
|                 | - CBA of marrow cell metaphases (at least 20 banded metaphases), to be performed at 3, 6 and 12 months until a CCyR has been achieved, then every 12 months. Once a CCyR is achieved, FISH on blood cells can be used. If an adequate molecular monitoring can be assured, cytogenetics can be spared. |

| Failure, progression | - RQ-PCR, mutational analysis, and CBA of marrow cell metaphases. Immunophenotyping in BP. |

| Warning | - Molecular and cytogenetic tests to be performed more frequently. CBA of marrow cell metaphases recommended in case of myelodysplasia or CCA/Ph- with chromosome 7 involvement. |

**Recommendations for cytogenetic and molecular monitoring.** The responses can be assessed either with molecular tests alone or with cytogenetic tests alone, depending on the local laboratory facilities, but whenever it is possible, both cytogenetic and molecular tests are recommended, until a CCyR and an MMR are achieved. Then, RQ-PCR alone may be sufficient. Mutational analysis by conventional Sanger sequencing is recommended in case of progression, failure and warning. In case of failure, warning, and of development of myelodysplastic features (unexpected leucopenia, thrombocytopenia, or anemia), CBA of marrow cell metaphases is recommended. FISH = Fluorescence-In-Situ-Hybridization. CCA/Ph- = Clonal Chromosome Abnormalities in Ph- cells.
European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013