

# Managing chronic myeloid leukemia for treatment-free remission: a proposal from the GIMEMA CML WP

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## Key Points

- In CML, the goals of treatment are survival and TFR.
- In this article, we suggest what treatment policies may be adopted to increase the rate of TFR.

Several papers authored by international experts have proposed recommendations on the management of BCR-ABL1<sup>+</sup> chronic myeloid leukemia (CML). Following these recommendations, survival of CML patients has become very close to normal. The next, ambitious, step is to bring as many patients as possible into a condition of treatment-free remission (TFR). The Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA; Italian Group for Hematologic Diseases of the Adult) CML Working Party (WP) has developed a project aimed at selecting the treatment policies that may increase the probability of TFR, taking into account 4 variables: the need for TFR, the tyrosine kinase inhibitors (TKIs), the characteristics of leukemia, and the patient. A Delphi-like method was used to reach a consensus among the representatives of 50 centers of the CML WP. A consensus was reached on the assessment of disease risk (EUTOS Long Term Survival [ELTS] score), on the definition of the most appropriate age boundaries for the choice of first-line treatment, on the choice of the TKI for first-line treatment, and on the definition of the responses that do not require a change of the TKI (BCR-ABL1 ≤10% at 3 months, ≤1% at 6 months, ≤0.1% at 12 months, ≤0.01% at 24 months), and of the responses that require a change of the TKI, when the goal is TFR (BCR-ABL1 >10% at 3 and 6 months, >1% at 12 months, and >0.1% at 24 months). These suggestions may help optimize the treatment strategy for TFR.

## Introduction

Tyrosine kinase inhibitors (TKIs) have been introduced in the therapy of chronic myeloid leukemia (CML) beginning with imatinib in 2001.<sup>1,2</sup> Four other TKIs have been approved between 2001 and 2013,<sup>3-6</sup> and are now available almost worldwide. The first attempt at establishing an internationally shared policy of treatment with TKIs was made by a panel of experts under the heading of the European Leukemia Network (ELN) in 2006,<sup>7</sup> revised in 2009<sup>8</sup> and 2013.<sup>9</sup> After 2013, other data have become available. The results of the IRIS trial, comparing imatinib with interferon- $\alpha$  (IFN $\alpha$ ), and of the trials comparing imatinib with the second-generation TKIs (2GTKIs) dasatinib and nilotinib, have been updated.<sup>10-12</sup> Moreover, the results of 2 trials comparing imatinib with another 2GTKI (bosutinib), several retrospective or prospective studies of different TKIs, and many comprehensive reviews<sup>13-33</sup> have been published. The ELN recommendations have not yet been updated. The National Comprehensive Cancer Network (NCCN)<sup>34</sup> regularly updates another set of treatment recommendations. The European Society for Medical Oncology has updated its recommendations in 2017.<sup>35</sup> The definitions of “optimal response” and “failure” (suggesting no treatment change or a switch to a different TKI, respectively) varied, but the primary goal of all recommendations thus far was to ensure the best survival. However, today, the expectation of patients and doctors has changed, and there is a trend to move the primary goal of CML treatment from survival to the achievement of a condition of treatment-free remission (TFR). Therefore, a debate on which treatment policies should be adopted for achieving TFR is open.

Over the last 20 years, the CML scenario has changed. Initially, due to the limited availability of TKIs and the rarity of the disease, only some referral centers could acquire a robust clinical experience. Today, the management of CML is extended to many centers, also small centers with limited experience, or even to individual practitioners. It is uncertain whether treating for TFR may be allowed in all centers and to every doctors, or if it is still investigational and should be limited to referral centers, but the possibility of achieving TFR can no longer be denied to any patient. The results of several phase 2 single-arm TFR studies,<sup>36-44</sup> individual experience, patient will, as well as commercial pressure, may bias the choice of treatment.<sup>13,24,26,45-48</sup> For these reasons, the CML Working Party (WP) of Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA; Italian Group for Hematologic Diseases of the Adult) has developed a project that has involved the representatives of 50 hematologic centers, with the purpose of suggesting a treatment policy aiming to the achievement of TFR.

## Material and methods

Fifty Italian centers, responsible for the care of >50% of the Italian CML patients, appointed a representative who participated actively in all steps of this project. A questionnaire addressing 326 key questions was circulated between July and September 2018. All 50 questionnaires were filled in and returned. The responses were analyzed, and the results were discussed in a first meeting held in October 2018. A second questionnaire with 70 questions was elaborated after the first meeting and a second meeting was held on April 2019. After that, the responses to a third questionnaire with 45 questions were analyzed for conclusions. During the meetings, the items receiving the consensus of >70% of panel members were

reviewed and finally approved by all members, sometimes with minor modifications. The items that had not received the consensus of >70% of panel members were discussed, and the results of the discussion were included in the second and the third questionnaire. After the analysis of the third questionnaire, the items that had reached a consensus of 70% or more were approved by all members and included in the list of the suggestions. When this consensus was not reached, it was acknowledged that neither evidence nor experience were sufficient to make proposals.

The project was not discussed or negotiated with the ELN panel, and, differently from the ELN recommendations, was specifically and entirely dedicated to the development of treatment policies finalized to TFR. M. Baccarani was no longer the coordinator of the ELN panel. Some senior panel members (M. Baccarani, F. Pane, G.R., G.S., and S. Soverini) who had been previously members of the ELN panel for CML recommendations were involved in the discussion, but they did not fill in the questionnaires. The methodology was quite similar to the Delphi technique.<sup>49</sup> All items were reviewed, discussed, and approved based on the interpretation of the available data by panel members and on their practice. The final proposals were not graded. No statistical procedures were used.

## Results

### Leukemia: risk

In the era of conventional chemotherapy, almost all patients died of leukemia. In 1984, a score predicting survival was elaborated by Sokal et al<sup>50</sup>; it became familiar worldwide, and was used in the majority of CML trials, until today because it was also able to predict response and survival in patients treated with IFN $\alpha$  and TKIs. Later on, 2 additional scores were proposed, based on patients treated with IFN $\alpha$  (EURO score)<sup>51</sup> and with imatinib (EUTOS score).<sup>52</sup> Considering that today many patients no longer die of leukemia,<sup>9,34</sup> a fourth risk score has been elaborated, to predict the probability of leukemia-related death (LRD)<sup>53</sup> in patients treated with imatinib, the new EUTOS Long Term Survival (ELTS) score. The ELTS score is based on simple hematologic data, spleen size, and age, just like the Sokal one. It predicts LRD better than Sokal, and the main difference is due to the fact that the negative prognostic weight of age is lower in TKI-treated patients (ELTS) than in patients treated with conventional chemotherapy (Sokal). Therefore, Sokal score classifies inappropriately more elderly patients than ELTS in the intermediate- and high-risk groups, and this is not useful for planning the intensity of treatment. A comparison of Sokal and ELTS scores is shown in Table 1. The panel suggests use of the new ELTS score to assess the baseline CML risk, and suggests that intermediate- and high-risk patients be grouped together.

Several other risk factors<sup>9,34</sup> have been identified, but so far none have entered into clinical use. An important exception is the presence of additional clonal chromosome abnormalities in Ph<sup>+</sup> cells (additional clonal chromosome abnormalities [ACA]/Ph<sup>+</sup>), including so far +8, +Ph, +19, +21, +17/i17, 11q23, abnormalities of chromosome 3 and 7, and complex karyotypes.<sup>56-62</sup> ACA/Ph<sup>+</sup> are associated with poor response to TKIs and higher rate of progression.<sup>56-62</sup> They should be enrolled in specifically designed trials. Presently, we suggest that they be classified and treated as high-risk patients.

### Patient: age

The age distribution of newly diagnosed patients with CML varies, particularly from western countries, where the median age is close

**Table 1. A summary of the main data comparing the application of the Sokal risk score and of the new ELTS risk score to newly diagnosed CML patients**

Reference*	No. of patients	TKI	Risk distribution, OS, and LRD	Low risk		Intermediate risk		High risk	
				SOKAL	ELTS	SOKAL	ELTS	SOKAL	ELTS
Pffirmann et al <sup>53</sup>	5154	Imatinib	% of patients	38	56	38	29	23	14
			10-y OS, %	89	88	81	79	75	68
			6-y LRD, %	3	2	4	5	8	12
Castagnetti et al <sup>54</sup>	904	Imatinib/ 2GTKI	% of patients	40	57	39	30	21	13
			8-y OS, %	95	94	85	81	84	61
			8-y LRD	2	2	6	9	10	14
Geelen et al <sup>55</sup>	709	Imatinib	% of patients	25	47	43	36	32	17
			8-y OS, %	NR	89	NR	67	NR	55
			8-y LRD, %	NR	1	NR	8	NR	5
	244	2GTKI	% of patients	27	49	41	35	32	16
			8-y OS, %	NR	92	NR	78	NR	77
			8-y LRD, %	NR	0	NR	0	NR	6

Sokal risk score<sup>50</sup>; the new ELTS risk score.<sup>53</sup> In all 3 studies, the ELTS score identified similar proportions of patients: 55%, 57%, 47%, and 49%, low; 28%, 30%, 36%, and 35%, intermediate; 13%, 13%, 17%, and 16%, high. In all 3 studies, the proportion of high-risk patients was higher with Sokal than with ELTS. This is due to the fact that age weighs more on Sokal than on ELTS calculation because, in the era of conventional chemotherapy, the prognostic value of age was higher than it is today in the TKI era. ELTS high-risk patients have an inferior OS and a superior LRD rate, as compared with Sokal high-risk ones. The calculation of the ELTS risk score is as follows:  $0.0025 \times (\text{age}/10)^3 + 0.0615 \times \text{spleen} + 0.1052 \text{ blasts} + 0.4104 \times (\text{platelet count}/1000)^{-0.5}$ , where age is in years, spleen in centimeters, maximum distance below costal margin, manual palpation, blasts are the percentage of blasts in blood.<sup>53</sup> Risk score: low,  $\leq 1.5680$ ; intermediate,  $1.5680 - \leq 2.2185$ ; high,  $> 2.2185$ .

LRD, leukemia-related death; NR, not reported; OS, overall survival.

\*Pffirmann et al<sup>53</sup> (5154 patients treated with imatinib); Castagnetti et al<sup>54</sup> (559 patients treated with imatinib, 345 pts treated with 2GTKIs, with no reported difference between imatinib and 2GTKIs), ASH 2018 (GIMEMA data); Geelen et al<sup>55</sup> (709 patients treated with imatinib and 244 patients treated with 2GTKIs) (Dutch and Swedish registries data).

to 60 years, to Asia and Africa, where the median age is lower than 50 years.<sup>63-65</sup> In Europe, <2% of patients are children or adolescents, ~15% are 18 to 40 years old, ~50% are 41 to 65 years old, ~25% are 66 to 80 years old, and ~6% are >80 years old. Age is an obvious determinant of life expectancy, is associated with comorbidities, and is also a prognostic factor of LRD.<sup>63-65</sup> However, and more importantly, it is the need for TFR that depends on age. Obviously, there are individual variations, but different ages are associated with different life-styles, different parental and family planning problems, different work conditions and career expectations, and different financial issues. The life of a young person is different from the life of an adult, of an elderly, and of a very elderly patient. Having settled that every patient may wish, and has the right, to achieve TFR, the need for TFR is related to age. Therefore, we suggest identifying 5 age groups: children and adolescents (<18 years old), young adults (18-40 years old), adults (41-65 years old), elderly (66-80 years old), and very elderly (>80 years old). It is important to notice that these age boundaries have no prognostic value and do not predict the probability of achieving TFR. Age is important because it is the best objective variable for the evaluation of the individual need for TFR, helping to choose the more convenient treatment policy for TFR. Defining age boundaries rises easy criticisms, but boundaries are always necessary: we all agree to use boundaries when defining responses, molecular, cytogenetic, and hematologic, and the risk score.

### Patient, health conditions, and comorbidities

General health conditions and several specific comorbidities, irrespective of the relationship with age, are important variables that may influence the treatment plan, particularly in the first-line.<sup>66</sup> For each TKI, the respective prescribing information alert that some comorbidities may represent a problem requiring careful monitoring, but do not mention specific contraindications. Many comorbidities

have been already identified.<sup>67</sup> The panel was asked to specify which comorbidities can represent an obstacle to the use of any particular TKI in first-line. A panel consensus was reached for nilotinib, dasatinib, and ponatinib. Strong contraindications to nilotinib and ponatinib include a history or a condition of ischemic heart disease, ranging from myocardial infarction to angina (symptomatic, or under medical treatment, or having required a coronary bypass or stents), of peripheral arterial thrombosis, of cerebrovascular events, and of diabetes mellitus. Strong contraindications to dasatinib include a history or a condition of a pleuropulmonary disease, including pulmonary fibrosis, respiratory failure, and pulmonary arterial hypertension. No strong contraindications were suggested for imatinib and bosutinib. If a change of the TKI is planned, in a second or a subsequent line, for resistance to the previous TKI, these comorbidities have only the value of an alert because the risk of leukemia progression may overcome the risk of complications.

### TKIs: efficacy

Four TKIs, imatinib, dasatinib, nilotinib, and bosutinib, have been approved and are available in first-line, without limitations, although the criteria for the reimbursability of these TKIs differ from country to country. The approval of 2 GTKIs was based on the 1-year results of company-sponsored registration trials<sup>3,4,6</sup> (Table 2). A 5-year update of these trials is available only for dasatinib and nilotinib.<sup>11,12</sup> The results can be summarized as follows: the patients treated with any of the 3 2GTKIs achieved faster and deeper molecular responses, as compared with those treated with imatinib. Progression-free survival (PFS) and overall survival (OS) at 5 years, and the rate of patients switching from the first-line TKI to another TKI, were almost the same with imatinib, dasatinib, and nilotinib. Such data are not yet available for bosutinib. Median age was 46 to 49 years in the DASISION<sup>4</sup> and ENESTnd<sup>3</sup> trials, and 52 to 53 years in the

**Table 2. The main 1-year results of the company-sponsored trials that were considered for approval of 2GTKIs in the first-line setting by the FDA and the EMA**

	ENESTnd		DASISION		BFORE	
	Imatinib	Nilotinib	Imatinib	Dasatinib	Imatinib	Bosutinib
Daily dose, mg	400 × 1	300 × 2	400 × 1	100 × 1	400 × 1	400 × 1
No. of patients	282	283	259	260	246	246
Median age, y	46	47	49	46	53	52
Low risk, %	37*	37*	33†	33†	39*	38*
Intermediate risk, %	36*	36*	48†	47†	39*	31*
High risk, %	28*	28*	19†	19†	21*	21*
CCyR, by 1 y	69%; <i>P</i> < .001	80%	72%; <i>P</i> < .001	83%	66%; <i>P</i> < .007	77%
MMR, at/by 1 y	at 22%; <i>P</i> < .001	44%	by 28%; <i>P</i> < .001	46%	at 37%; <i>P</i> = .02	47%
D/C, in 5 y	50%	40%	37%	39%		
MMR, by 5 y	60%; <i>P</i> < .0001	77%	66%; <i>P</i> = 0.0002	76%		
MR 4.0, by 5 y	42%; <i>P</i> < .0001	66%		NR		
MR 4.5, by 5 y	31%; <i>P</i> < .0001	54%	33%; <i>P</i> = .02	42%		
PFS, 5-y	91%	92%	85%	86%		
OS, 5-y	92%	94%	90%	91%		
LRD, 5-y	6%; <i>P</i> = .02	2%		NR		

For ENESTnd<sup>11</sup> and DASISION,<sup>12</sup> also the follow-up results, at 5 years, are shown, confirming a higher rate and depth of molecular response, but showing no superiority in PFS and OS. From the ENESTnd study, a small but significant difference in leukemia-related deaths was also reported.

at, the proportion of patients with that response at 1 year; by, cumulative incidence of that response after 1 year or 5 years; CCyR, complete cytogenetic response ( $Ph^+$  0); D/C, discontinued for ever the treatment assigned; EMA, European Medicine Agency; FDA, Federal Drug Administration; MMR, major molecular response ( $BCR-ABL1 \leq 0.1\%$ )<sup>15</sup>; MR 4.0,  $BCR-ABL1 \leq 0.01\%$ <sup>15</sup>; MR 4.5,  $BCR-ABL1 \leq 0.0032\%$ <sup>15</sup>; PFS, progression-free survival.

\*Sokal risk.

†EURO risk.

BFORE trial,<sup>6</sup> far less than the median age of unselected newly diagnosed patients. This point is important because these results may be erroneously interpreted as a general superiority of 2GTKIs, whereas superiority was found in an age-selected population of young and adult patients, so that the difference cannot be extended as such to all patients. A fifth TKI, ponatinib, has been approved (PACE study)<sup>5</sup> only in second-line (in some countries after failure of 2GTKIs, in some countries also after imatinib failure), or in patients with the T315I mutation. There are no studies comparing a 2GTKI with another 2GTKI, either in first-line or in second-line.

### TKIs, toxicity, and tolerability

Toxicity and tolerability have been the object of a recent, comprehensive, critical review.<sup>67</sup> It is relevant to consider that all the comparative trials were designed, sponsored, performed, and analyzed by companies that had an obvious interest in the development of 2GTKIs. Moreover, in all registration studies, the criteria for patient selection, particularly age and comorbidities, and the rigid criteria of treatment adaptation, limit the applicability of the results to “real-life” patients. Toxicity and tolerability were compared only between imatinib and 2GTKIs because there are no studies comparing the 2GTKIs. Based on the interpretation of the available data and on the experience matured with practice, the panel has concluded that nilotinib and ponatinib may expose the patient to metabolic and cardiovascular toxicity, and dasatinib to pleuropulmonary toxicity, whereas the toxicity of imatinib and bosutinib is generally weak, although it may affect considerably the quality of life. Concerning tolerability, the side effects are different according to the TKI, but no major differences were identified, and no consensus was reached.

### TKIs: dose

All TKIs were approved and registered at a fixed dose. A change of the dose is allowed only in case of toxicity or tolerability. Some studies have stressed the importance of taking always the full registered dose and have highlighted the problem of compliance.<sup>68,69</sup> Compliance is important and all patients should take the standard dose, whenever tolerated. However, it has not been confirmed that a full dose is necessary in all patients, when the dose is adapted to tolerance.<sup>70-72</sup> Because the relationship between the dose and the response can easily be monitored, the panel agreed that greater flexibility should be allowed for the use of TKIs at a reduced dose,<sup>73</sup> so that in a patient who cannot tolerate the standard full dose, but has achieved an optimal response, the TKI dose should not be increased.

### TKIs: cost

The costs of the TKIs are very different, but are always a heavy financial burden with the exception of the generic formulations of imatinib.<sup>74-76</sup> In Italy, the yearly cost ranges from a few hundreds euro for generic imatinib, to ~10 000 euro for branded imatinib (Glivec), ~35 000 euro for nilotinib (Tasigna), ~45 000 euro for dasatinib (Sprycel) and bosutinib (Bosulif), and ~75 000 euro for ponatinib (Iclusig). Generic, cheaper formulations of nilotinib and dasatinib will soon be available.

### Response assessment: monitoring

The response is evaluated by cytogenetic and/or molecular tests.<sup>77</sup> Cytogenetic monitoring requires at least 2 or 3 marrow biopsies, starting from the third month until the achievement of a complete

**Table 3. The definition of response to first-line treatment, as proposed by the panel, when TFR is the primary goal**

	Optimal	Nonoptimal	Failure/resistance
	Continue the same TKI	Switching to another TKI is optional	Changing the TKI is mandatory
3 mo	CHR, and BCR-ABL1 $\leq 10$ , or BCR-ABL1 $> 10$ , not confirmed	NA	No CHR, or BCR-ABL1 $> 10$ , confirmed
6 mo	BCR-ABL1 $\leq 1$	BCR-ABL1 $> 1-10$	BCR-ABL1 $> 10$
12 mo	BCR-ABL1 $\leq 0.1$	BCR-ABL1 $> 0.1-1$	BCR-ABL1 $> 1$
24 mo	BCR-ABL1 $\leq 0.01$	BCR-ABL1 $> 0.01-0.1$	BCR-ABL1 $> 0.1$ or an increase of BCR-ABL1 of at least 1 log or a mutation

If the BCR-ABL1 level at 3 months is  $> 10\%$ , the qPCR must be repeated immediately. If it decreases to  $< 10\%$ , the response becomes optimal; if it remains  $> 10\%$ , the response becomes a failure. Notice that a more precise definition of the molecular response at 3 months is not only beneficial for the patients, but is also cost-effective because the cost of an extra qPCR is fully covered by the differences in cost between imatinib and 2GTKIs.

CHR, complete hematological response; NA, not applicable.

cytogenetic response (CCyR), to obtain the cells for chromosome banding analysis (CBA) of at least 20 marrow cell metaphases.<sup>77</sup> The panel acknowledged the historic importance of cytogenetic monitoring, but reached a full consensus that cytogenetics alone is no longer sufficient for disease monitoring. However, cytogenetics is always mandatory at baseline, as well as in case of treatment failure and in some selected cases, like in cases with ACA/Ph<sup>+</sup> at baseline, and cases with atypical transcripts that cannot be quantified. Instead, molecular monitoring requires only a blood sample. It is based on a standardized assay, real-time quantitative polymerase chain reaction (qPCR), which has been internationally recognized, used and validated for  $> 10$  years.<sup>78-81</sup> A qPCR should be performed at least every 3 months. Longer intervals would compromise the control of leukemia in the patients who have not achieved a major molecular response (MMR), and would not be sufficient to assess the

stability of deep molecular response (DMR) in the patients who may become eligible for TFR.

### Response to first-line treatment

The 2013 ELN recommendations<sup>9</sup> proposed defining the response as optimal and failure. In the NCCN guidelines,<sup>34</sup> the ELN definition of optimal corresponds to the recommendation to continue the same TKI, whereas the ELN definition of failure corresponds to the suggestion to change the TKI. There are data showing that failure on imatinib can be successfully rescued with 2GTKIs, whereas there are less data in cases of failure on 2GTKIs. However, also in this case, the switch to another 2GTKI is necessary. The ELN suggested a third type of response, "warning," formerly "sub-optimal," as an alert suggesting a closer monitoring of the response. This definition may be useful for the early response, but not for later responses. We propose substituting "warning" with "nonoptimal,"

**Table 4. A comparison of the classification of the response in the first-line setting, with the ELN 2013 and the NCCN 1.2019 classifications**

	Optimal			Warning or nonoptimal			Failure		
	ELN 2013	GIMEMA 2019	NCCN 1.2019	ELN 2013	GIMEMA 2019	NCCN 1.2019	ELN 2013	GIMEMA 2019	NCCN 1.2019
Baseline	NA	NA	NA	High risk, or CCA/Ph <sup>+</sup> , major route	NA	NA	NA	NA	NA
3 mo	BCR-ABL1 $\leq 10\%$ or Ph <sup>+</sup> $\leq 35\%$	BCR-ABL1 $\leq 10\%$ or BCR-ABL1 $> 10\%$ , not confirmed	BCR-ABL1 $< 10\%$	BCR-ABL1 $> 10\%$ , or Ph <sup>+</sup> 35%-95%	NA	BCR-ABL1 $> 10\%$	No CHR, or Ph <sup>+</sup> $> 95\%$	No CHR, or BCR-ABL1 $> 10\%$ confirmed	NA
6 mo	BCR-ABL1 $\leq 1\%$ or Ph <sup>+</sup> 0	BCR-ABL1 $\leq 1\%$	BCR-ABL1 $< 10\%$	BCR-ABL1 1%-10% or Ph <sup>+</sup> 1%-35%	BCR-ABL1 $> 1\%-10\%$	NA	BCR-ABL1 $> 10\%$ or Ph <sup>+</sup> $> 35\%$	BCR-ABL1 $> 10\%$	BCR-ABL1 $> 10\%$
12 mo	BCR-ABL1 $\leq 0.1\%$	BCR-ABL1 $\leq 0.1\%$	BCR-ABL1 $\leq 1\%$	BCR-ABL1 0.1%-1%	BCR-ABL1 $> 0.1\%-1\%$	BCR-ABL1 $> 1\%-10\%$	BCR-ABL1 $> 1\%$ or Ph <sup>+</sup> $> 0$	BCR-ABL1 $> 1\%$	BCR-ABL1 $> 10\%$
Then*	BCR-ABL1 $\leq 0.1\%$	BCR-ABL1 $\leq 0.01\%$	BCR-ABL1 $\leq 1\%$	CCA/Ph <sup>-</sup> (-7, 7q-) )	BCR-ABL1 $> 0.01\%-0.1\%$	NA	Loss of CHR, or CCyR, or MMR, or mutations, or CCA/Ph <sup>+</sup>	BCR-ABL1 $> 0.1\%$ or mutations, or BCR-ABL1 increase of $> 1$ log	BCR-ABL1 $> 1\%$

ELN 2013 and the NCCN 1.2019 classifications.<sup>9,34</sup> Notice that for the GIMEMA classification it is mandatory to repeat immediately the qPCR if at 3 months the BCR-ABL1 level is  $> 10\%$ . If the BCR-ABL1 level drops to  $\leq 10\%$ , the response turns to optimal. If it is confirmed to be  $> 10\%$ , the response turns to failure/resistance. Therefore, the GIMEMA classification does not foresee a "nonoptimal" response at 3 months. The cost of an extra qPCR not only allows the patient to make the best choice, but is also fully covered by the cost differences between imatinib and 2GTKIs. At baseline, high-risk and clonal chromosome abnormalities (CCA)/Ph<sup>+</sup> are no longer classified as "warning" because they are included in the high-risk treatment group. The ELN term "warning" is substituted by the term "nonoptimal." This is not a trivial difference because the meaning of "warning" was "be careful and monitor the response more frequently," whereas "nonoptimal" means that it opens an option for a switch, depending not only on the response but also on the patients (age, health conditions, comorbidities, quality of life, etc). At 6 and 12 months, the GIMEMA and ELN 2013 classifications are identical. After 12 months, the GIMEMA panel has agreed on more stringent definitions of optimal response, from BCR-ABL1  $\leq 0.1\%$  to BCR-ABL1  $\leq 0.01\%$  for optimal response, and from BCR-ABL1  $> 1\%$  to BCR-ABL1  $> 0.1\%$  for failure. The 1.2019 NCCN criteria are much less stringent because after 1 year (at 15 months) only a BCR-ABL1 level  $> 1\%$  mandates a change of treatment. Notice that GIMEMA definitions refer to TFR, whereas ELN and NCCN definitions refer to survival.

\*At any time for ELN 2013, at 24 months for GIMEMA, at 15 months for NCCN 1.2019.

**Table 5. A simplified evaluation of the response to treatment in the second and subsequent lines of treatment**

Response to	
<b>Second-line TKI</b>	
In case of failure, toxicity, or intolerance	Same as response to first-line
In case of early switch (6 and 12 mo) for nonoptimal response	Same as response to first-line
In case of late switch for nonoptimal response	Personalized evaluation
Third- or fourth-line TKI	Personalized evaluation

where “nonoptimal” is not an alert, but opens an option for a switch, the decision of switching depending on the characteristics of the patients (age, health conditions, comorbidities, quality of life, etc). The proposed classification of the response to first-line treatment is shown in Table 3. A comparison of this classification with the ELN 2013 and the NCCN 1.2019 classifications is shown and commented on in Table 4.

### Response to second-line and subsequent lines of treatment

The definition of the response to second- and subsequent lines of treatment is useful because up to 50% of newly diagnosed patients may change the first TKI, sooner or later, for several reasons. Because TFR may similarly be the main goal of second-line treatment, the panel agreed to suggest that the response to second-line should be monitored and classified like the response to first-line (Table 5). In third and fourth line, and in case of a late switching in search of a deeper molecular response, the panel agreed that neither

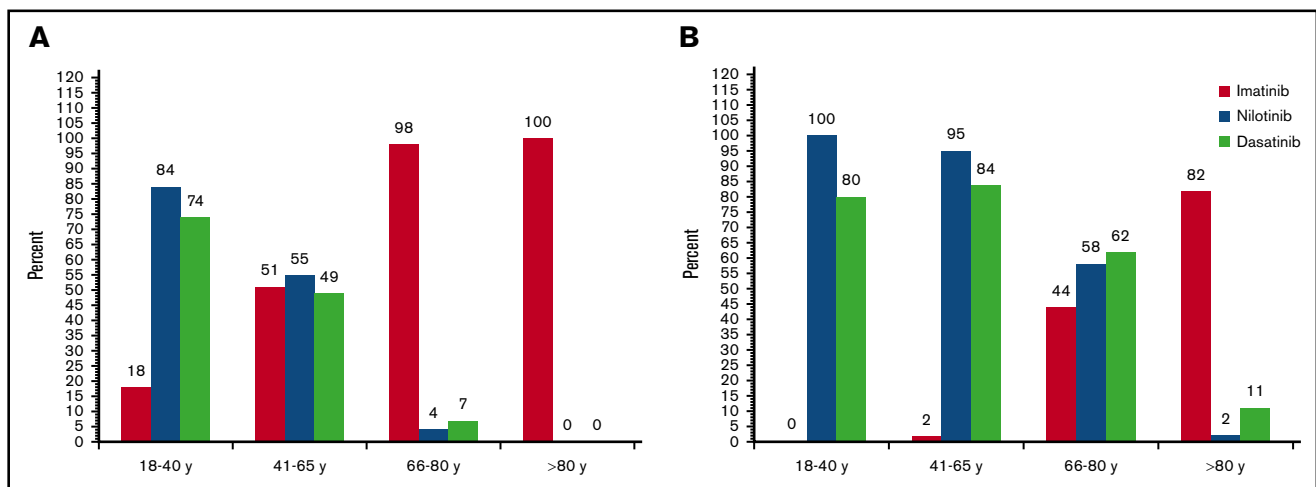
evidence nor experience were sufficient to make specific recommendations, so that a personalized evaluation of any single patient is more appropriate.

### The choice of the TKI: first-line setting

The choice of the first-line TKI has not yet been settled, and is a matter of debate.<sup>9,34,82,83</sup> Panel members were required to indicate which TKI they are currently prescribing in the first-line setting. The responses are shown in Figure 1, as a percentage of the answers of panel members. Because several members indicated >1 TKI, the total of the responses may exceed 100%. A consensus was reached for the choice of a 2GTKIs, in all young patients (18-40 years) and in intermediate- and high-risk adult patients (41-65 years), and for the choice of imatinib, in low-risk elderly patients (66-80 years) and in all very elderly patients (>80 years). However, in low-risk adults (41-65 years) and in intermediate- and high-risk elderly patients (66-80 years), a consensus was not reached. It should be noticed that the 2013 ELN recommendations did not assign a priority to any TKI. The 1.2019 NCCN guidelines did not assign a priority for low-risk patients, irrespective of age, but suggested some priority to 2GTKIs, including bosutinib, in high- and intermediate-risk ones, not elderly.

### The choice of the TKI: after first-line

All TKIs were approved for second-line treatment based on company-sponsored, phase 2, single-arm trials.<sup>84</sup> No academic, investigator-initiated studies have addressed a comparison among the available TKIs. Therefore, the data are not sufficient to make suggestions regarding the choice of the TKI in the second- or subsequent-line setting, apart from the differential sensitivity in patients with the presence of BCR-ABL1 point mutations (Table 6). Because the



**Figure 1. Choice of TKIs in the first-line setting.** (A) Percentage of low-risk patients. (B) Percentage of intermediate- plus high-risk patients. The indications of 50 panel members for the choice of the TKI in the first-line setting, according to age and to ELTS risk, in the absence of strong contraindications to dasatinib or nilotinib, are shown. The numbers over the bars express the proportion of panel members who have assigned priority to each TKI, respectively. With 1 exception (>80 years, low risk), the total of the numbers over the columns is higher than 100% because several panel members indicated >1 TKI. Some panel members also included bosutinib, although data and experience with bosutinib are still limited. A consensus for 2GTKIs (dasatinib or nilotinib) was reached in all young patients (18-40 years old) and in intermediate- plus high-risk adult patients (41-65 years old). A consensus for imatinib was reached in low-risk elderly patients (66-80 years old) and in all very elderly patients (>80 years old). No consensus was reached in intermediate- plus high-risk adult (41-65 years old) and elderly patients (66-80 years old). Low-risk patients account for ~10%, 30%, 15%, and 4% in each age group, whereas intermediate- and high-risk patients account for ~6%, 20%, 10%, and 3%, respectively, in each age group. Notice that the 2013 ELN recommendations did not assign any priority to any TKI. Also, the 1.2019 NCCN guidelines did not assign any priority as far as low-risk patients are concerned, irrespective of age, but suggested some priority for 2GTKIs, including bosutinib, in high- and intermediate-risk ones, not elderly.

**Table 6. List of the 35 most frequent BCR-ABL1 kinase domain mutations associated with resistance to TKIs (based on the integration of in vitro IC<sub>50</sub> data and in vivo observations)**

Mutation	TKI(s) to which the mutation confers resistance
M244V	Imatinib
L248V	Imatinib
G250E	Imatinib
Q252H	Imatinib
Y253H	Imatinib, nilotinib
E255V	Imatinib, nilotinib, bosutinib
E255K	Imatinib, nilotinib, bosutinib
L273M	Imatinib
D276G	Imatinib
T277A	Imatinib
E279K	Imatinib
V299L	Dasatinib, bosutinib
F311L	Imatinib
T315I	Imatinib, nilotinib, dasatinib, bosutinib
T315A	Dasatinib
T315M	Ponatinib
T315L	Ponatinib
F317L	Imatinib, dasatinib
F317V	Imatinib, dasatinib
F317I	Imatinib, dasatinib
F317C	Imatinib, dasatinib
M351T	Imatinib
E355G	Imatinib
F359C	Imatinib, nilotinib
F359I	Imatinib, nilotinib
F359V	Imatinib, nilotinib
E379K	Imatinib
L384M	Imatinib
L387M	Imatinib
L387F	Imatinib
H396R	Imatinib
H396P	Imatinib
E459K	Imatinib
F486S	Imatinib

detection of a mutation is the only factor that can specifically guide the choice of another TKI,<sup>85</sup> when a switch is planned for resistance/failure, a mutational analysis should always be performed using at least Sanger sequencing (SS), and whenever possible using next-generation sequencing (NGS), which is not yet widely available, but being more sensitive than SS<sup>86-90</sup> can avoid a wrong choice in up to 25% of cases. Whether mutational analysis should be performed in the case of nonoptimal response has been debated, but a consensus was not reached. Apart from mutations, the characteristics of the patient (age and comorbidities) and the toxicity profile of the TKIs count.

### The switch from first-line

In the case of failure/resistance, at any time point, including 3 months, the change of the TKI is appropriate, also if the first-line TKI was

a 2GTKI. In the case of nonoptimal response, the change from a TKI to another TKI is optional, if it is believed that it may help to achieve a deeper molecular response and to bring the patient to TFR. There are some data,<sup>20,26,32,43</sup> and there is some experience, of switching from imatinib to a 2GTKI, not from a 2GTKI to another TKI. All studies suggest that such a switch may increase the rate of deep molecular response (DMR), hence the number of patients eligible for treatment discontinuation and TFR, but, regrettably, all of these studies are single-arm and do not allow for calculation of the benefit of a switching policy against the risk of increased toxicity. The panel did not reach a consensus, either pro or con.

### Treatment discontinuation and TFR

Many studies, some retrospective and some prospective, have shown beyond any doubt that a consistent proportion, ranging between 30% and 70%, of the patients who discontinue treatment after having achieved a DMR (MR 4.0, BCR-ABL1  $\leq 0.01\%$ <sup>IS</sup>, or MR 4.5, BCR-ABL1  $\leq 0.0032\%$ <sup>IS</sup>) may remain treatment-free for an as-yet undefined period of time.<sup>36-48</sup> It is important to underline that the patients with molecular relapse after discontinuation do not progress, and are almost all able to achieve DMR again upon retreatment, and that some of them can become eligible for a second attempt of treatment discontinuation. The probability of achieving TFR may depend on several factors: leukemia or patient characteristics, TKI type, treatment duration, DMR duration, etc.<sup>36-48</sup> Based on the interpretation of the available data and on their experience, the panel members agreed that neither age nor risk are relevant. To ensure safety and avoid disease progression, the minimum duration of treatment should be 3 years with a 2GTKI and 5 years with imatinib. The minimum duration of a stable DMR should be 2 years, with any TKI. There was no consensus on the "optimal" duration of treatment and of DMR, as well as on the depth of the molecular response, MR 4.0 or MR 4.5. After discontinuation, patients must be monitored monthly by qPCR for at least 6 months,<sup>26,37-44,47</sup> but there was no consensus on the frequency of monitoring after the first 6 months, either monthly, or bimonthly, or every 3 months.

### Pregnancy: conception

Safe parenting, an important goal of a treatment policy aiming at TFR, has been the subject of recent reviews.<sup>91,92</sup> The panel agreed that TKIs should not be used during pregnancy due to their potential teratogenicity, and must be discontinued as soon as the pregnancy starts. Pregnancy can also be planned in the case of MMR, provided that the MMR has been stable for a minimum of 2 years, and that treatment has been stopped. For male patients, the panel agreed that imatinib, dasatinib, and nilotinib should not be stopped. However, male patients should be advised that data on bosutinib and ponatinib are not yet sufficient.

### Discussion

The first pivotal report on TFR was published in 2007.<sup>36</sup> Since then, the interest in TFR has increasingly grown. However, regrettably, no trials were performed to compare the efficacy of different treatment policies and different TKIs for TFR, with the exception of an ongoing GIMEMA trial (SUSTRENIM), investigating the 5-year TFR rate in newly diagnosed CML patients treated first-line with nilotinib or with imatinib followed by switch to nilotinib in the case of nonoptimal response.<sup>93</sup> SUSTRENIM results will be available not earlier than

3 years from now, so the debate is still open. Strong pressure exists toward privileging TFR over privileging survival, resulting in a kind of equilibrium that on one hand may be wise, but on the other hand is ambiguous, implying subjective decisions. The GIMEMA CML WP has privileged TFR over survival, as the main goal, for virtually all patients, and has undertaken a project ending with specific treatment suggestions for safe achievement of TFR, preserving patients from exposure to unnecessary potentially more toxic drugs, but maximizing the probabilities of achieving TFR.

Age boundaries have been proposed not for the prognostic value of age, but considering age as a measure of the need of achieving TFR. Strong comorbidities were identified because they are a factor as important as the potency of the TKI, for the choice of the TKI in the first-line setting. For the first time, a specific suggestion has been made on the choice of the first-line TKI. The definitions of the response to first-line treatment, especially at 3 and 24 months, were made more stringent, and were also adopted for the definition of the response to second-line treatment. It is not yet clear whether the same definitions should also be adopted when the primary goal is survival, in patients where TFR cannot be achieved. Sometimes, the data are still incomplete or missing, and the opinions are different, so that it has been acknowledged that sometimes neither evidence nor experience were sufficient to make a suggestion. The debate on the cost-to-benefit ratio of using 2GTKs is still open, and is hot.<sup>76,94</sup> Our suggestions are not guidelines, and have no professional or legal implications, but may help optimize the treatment of CML for TFR, not only increasing the TFR rate but also limiting toxicity and controlling the cost.

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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*. 2001;344(14):1031-1037.
2. O'Brien SG, Guilhot F, Larson RA, et al; IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348(11):994-1004.
3. Saglio G, Kim D-W, Issaragrisil S, et al; ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2251-2259.
4. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2260-2270.
5. Cortes JE, Kim D-W, Pinilla-Ibarz J, et al; PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369(19):1783-1796.
6. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. *J Clin Oncol*. 2018;36(3):231-237.
7. Baccarani M, Saglio G, Goldman J, et al; European LeukemiaNet. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*. 2006;108(6):1809-1820.
8. Baccarani M, Cortes J, Pane F, et al; European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol*. 2009;27(35):6041-6051.
9. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-884.
10. Hochhaus A, Larson RA, Guilhot F, et al; IRIS Investigators. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med*. 2017;376(10):917-927.

## Authorship

Contribution: M. Baccarani, S. Soverini, E.A., M. Bonifacio, M. Breccia, F. Castagnetti, F. Pane, D. Russo, G.S., P.V., and G.R. designed the project and formulated the questions to GIMEMA panel members; M. Baccarani, S. Soverini, F. Castagnetti, and G.R. collected and ordered the answers to the questions; M. Baccarani, F. Castagnetti, and G.R. calculated the consensus and formulated the proposals; M. Baccarani, S. Soverini, F. Castagnetti, and G.R. wrote the manuscript; and all coauthors filled in the questionnaires, participated personally in the meetings, revised the manuscript, and approved the final version of the manuscript.

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11. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia*. 2016;30(5):1044-1054.
12. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: The dasatinib versus imatinib study in treatment-naive chronic myeloid leukemia patients trial. *J Clin Oncol*. 2016;34(20):2333-2340.
13. Hughes T, White D. Which TKI? An embarrassment of riches for chronic myeloid leukemia patients. *Hematology Am Soc Hematol Educ Program*. 2013; 2013:168-175.
14. Rousselot P, Cony-Makhoul P, Nicolini F, et al; French Intergroup For Chronic Myelogenous Leukemia (Fi-LMC). Long-term safety and efficacy of imatinib mesylate (Gleevec®) in elderly patients with chronic phase chronic myelogenous leukemia: results of the AFR04 study. *Am J Hematol*. 2013;88(1):1-4.
15. Hehlmann R, Müller MC, Lauseker M, et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. *J Clin Oncol*. 2014;32(5):415-423.
16. Castagnetti F, Gugliotta G, Breccia M, et al; GIMEMA CML Working Party. Long-term outcome of chronic myeloid leukemia patients treated frontline with imatinib. *Leukemia*. 2015;29(9):1823-1831.
17. Hughes TP, Lipton JH, Spector N, et al. Deep molecular responses achieved in patients with CML-CP who are switched to nilotinib after long-term imatinib. *Blood*. 2014;124(5):729-736.
18. Jain P, Kantarjian H, Alattar ML, et al. Long-term molecular and cytogenetic response and survival outcomes with imatinib 400 mg, imatinib 800 mg, dasatinib, and nilotinib in patients with chronic-phase chronic myeloid leukaemia: retrospective analysis of patient data from five clinical trials. *Lancet Haematol*. 2015;2(3):e118-e128.
19. Sasaki K, Strom SS, O'Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. *Lancet Haematol*. 2015;2(5):e186-e193.
20. Yeung DT, Osborn MP, White DL, et al; Australasian Leukaemia and Lymphoma Group. TIDEL-II: first-line use of imatinib in CML with early switch to nilotinib for failure to achieve time-dependent molecular targets. *Blood*. 2015;125(6):915-923.
21. Wang J, Shen Z-X, Saglio G, et al. Phase 3 study of nilotinib vs imatinib in Chinese patients with newly diagnosed chronic myeloid leukemia in chronic phase: ENESTchina. *Blood*. 2015;125(18):2771-2778.
22. Gugliotta G, Castagnetti F, Breccia M, et al; GIMEMA CML Working Party. Rotation of nilotinib and imatinib for first-line treatment of chronic phase chronic myeloid leukemia. *Am J Hematol*. 2016;91(6):617-622.
23. Hochhaus A, Rosti G, Cross NCP, et al. Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the European ENEST1st study. *Leukemia*. 2016;30(1):57-64.
24. Rosti G, Castagnetti F, Gugliotta G, Baccarani M. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? *Nat Rev Clin Oncol*. 2017;14(3):141-154.
25. Lipton JH, Chuah C, Guerci-Bresler A, et al; EPIC investigators. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17(5):612-621.
26. Hughes TP, Ross DM. Moving treatment-free remission into mainstream clinical practice in CML. *Blood*. 2016;128(1):17-23.
27. Castagnetti F, Di Raimondo F, De Vivo A, et al. A population-based study of chronic myeloid leukemia patients treated with imatinib in first line. *Am J Hematol*. 2017;92(1):82-87.
28. Geelen IGP, Thielen N, Janssen JJWM, et al. Treatment outcome in a population-based, "real-world" cohort of patients with chronic myeloid leukemia. *Haematologica*. 2017;102(11):1842-1849.
29. Hehlmann R, Lauseker M, Sauße S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. *Leukemia*. 2017;31(11):2398-2406.
30. Hoffmann VS, Baccarani M, Hasford J, et al. Treatment and outcome of 2904 CML patients from the EUTOS population-based registry. *Leukemia*. 2017; 31(3):593-601.
31. Hoffmann VS, Hasford J, Deininger M, Cortes J, Baccarani M, Hehlmann R. Systematic review and meta-analysis of standard-dose imatinib vs. high-dose imatinib and second generation tyrosine kinase inhibitors for chronic myeloid leukemia. *J Cancer Res Clin Oncol*. 2017;143(7):1311-1318.
32. Hughes TP, Leber B, Cervantes F, et al. Sustained deep molecular responses in patients switched to nilotinib due to persistent BCR-ABL1 on imatinib: final ENESTcmr randomized trial results. *Leukemia*. 2017;31(11):2529-2531.
33. Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*. 2018;132(4):393-404.
34. Radich JP, Deininger M, Abboud CN, et al. Chronic myeloid leukemia, version 1.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018;16(9):1108-1135.
35. Hochhaus A, Saussele S, Rosti G, et al; ESMO Guidelines Committee. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl 4):iv41-iv51.
36. Mahon F-X, Réa D, Guilhot J, et al; Intergroupe Français des Leucémies Myéloïdes Chroniques. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*. 2010;11(11):1029-1035.
37. Rousselot P, Charbonnier A, Cony-Makhoul P, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol*. 2014;32(5): 424-430.

38. Ross DM, Branford S, Seymour JF, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*. 2013;122(4):515-522.
39. Etienne G, Guilhot J, Rea D, et al. Long-term follow-up of the French Stop Imatinib (STIM1) study in patients with chronic myeloid leukemia. *J Clin Oncol*. 2017;35(3):298-305.
40. Hochhaus A, Masszi T, Giles FJ, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. *Leukemia*. 2017;31(7):1525-1531.
41. Legros L, Nicolini FE, Etienne G, et al; French Intergroup for Chronic Myeloid Leukemias. Second tyrosine kinase inhibitor discontinuation attempt in patients with chronic myeloid leukemia. *Cancer*. 2017;123(22):4403-4410.
42. Rea D, Nicolini FE, Tulliez M, et al; France Intergroupe des Leucémies Myéloïdes Chroniques. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. *Blood*. 2017;129(7):846-854.
43. Takahashi N, Nishiwaki K, Nakaseko C, et al; STAT study group. Treatment-free remission after two-year consolidation therapy with nilotinib in patients with chronic myeloid leukemia: STAT2 trial in Japan. *Haematologica*. 2018;103(11):1835-1842.
44. Saussele S, Richter J, Guilhot J, et al; EURO-SKI investigators. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19(6):747-757.
45. Sauße S, Richter J, Hochhaus A, Mahon F-X. The concept of treatment-free remission in chronic myeloid leukemia. *Leukemia*. 2016;30(8):1638-1647.
46. Baccarani M. Treatment-free remission in chronic myeloid leukemia: floating between expectation and evidence. *Leukemia*. 2017;31(4):1015-1016.
47. Rea D, Ame S, Berger M, et al; French Chronic Myeloid Leukemia Study Group. Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia: Recommendations for clinical practice from the French Chronic Myeloid Leukemia Study Group. *Cancer*. 2018;124(14):2956-2963.
48. Mori S, Vagge E, le Coutre P, et al. Age and dPCR can predict relapse in CML patients who discontinued imatinib: the ISAV study. *Am J Hematol*. 2015;90(10):910-914.
49. Linstone HA. The Delphi technique. Handbook of Futures research. Westport, CT: Greenwood; 1978.
50. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood*. 1984;63(4):789-799.
51. Hasford J, Pfirrmann M, Hehlmann R, et al; Writing Committee for the Collaborative CML Prognostic Factors Project Group. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. *J Natl Cancer Inst*. 1998;90(11):850-858.
52. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. *Blood*. 2011;118(3):686-692.
53. Pfirrmann M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia*. 2016;30(1):48-56.
54. Castagnetti F, Gugliotta G, Breccia M, et al. The use of the EUTOS long-term survival score is strongly advised in elderly chronic myeloid leukemia patients [abstract]. *Blood*. 2018;132(suppl 1). Abstract 44.
55. Geelen IGP, Sandin F, Thielen N, et al. Validation of the EUTOS long-term survival score in a recent independent cohort of "real world" CML patients. *Leukemia*. 2018;32(10):2299-2303.
56. Fabarius A, Leitner A, Hochhaus A, et al; Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) and the German CML Study Group. Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: long-term observation of 1151 patients from the randomized CML Study IV. *Blood*. 2011;118(26):6760-6768.
57. Luatti S, Castagnetti F, Marzocchi G, et al; Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Working Party on CML. Additional chromosomal abnormalities in Philadelphia-positive clone: adverse prognostic influence on frontline imatinib therapy: a GIMEMA Working Party on CML analysis [published correction appears in *Blood*. 2013;121(26):5259]. *Blood*. 2012;120(4):761-767.
58. Fabarius A, Kalmanti L, Dietz CT, et al; SAKK and the German CML Study Group. Impact of unbalanced minor route versus major route karyotypes at diagnosis on prognosis of CML. *Ann Hematol*. 2015;94(12):2015-2024.
59. Wang W, Cortes JE, Lin P, et al. Clinical and prognostic significance of 3q26.2 and other chromosome 3 abnormalities in CML in the era of tyrosine kinase inhibitors. *Blood*. 2015;126(14):1699-1706.
60. Wang W, Cortes JE, Lin P, et al. Impact of trisomy 8 on treatment response and survival of patients with chronic myelogenous leukemia in the era of tyrosine kinase inhibitors. *Leukemia*. 2015;29(11):2263-2266.
61. Wang W, Cortes JE, Tang G, et al. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. *Blood*. 2016;127(22):2742-2750.
62. Alhurajji A, Kantarjian H, Boddu P, et al. Prognostic significance of additional chromosomal abnormalities at the time of diagnosis in patients with chronic myeloid leukemia treated with frontline tyrosine kinase inhibitors. *Am J Hematol*. 2018;93(1):84-90.
63. Gugliotta G, Castagnetti F, Palandri F, et al; Gruppo Italiano Malattie Ematologiche dell'Adulto CML Working Party. Frontline imatinib treatment of chronic myeloid leukemia: no impact of age on outcome, a survey by the GIMEMA CML Working Party. *Blood*. 2011;117(21):5591-5599.
64. Castagnetti F, Gugliotta G, Baccarani M, et al; GIMEMA CML Working Party. Differences among young adults, adults and elderly chronic myeloid leukemia patients. *Ann Oncol*. 2015;26(1):185-192.
65. Hoffmann VS, Baccarani M, Hasford J, et al. The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European Countries. *Leukemia*. 2015;29(6):1336-1343.
66. Saussele S, Krauss MP, Hehlmann R, et al; Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung and the German CML Study Group. Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV. *Blood*. 2015;126(1):42-49.

67. Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia*. 2016;30(8):1648-1671.
68. Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood*. 2009;113(22):5401-5411.
69. Marin D, Bazeos A, Mahon F-X, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic response on imatinib. *J Clin Oncol*. 2010;28(14):2381-2388.
70. Fassoni AC, Baldow C, Roeder I, Glauche I. Reduced tyrosine kinase inhibitor dose is predicted to be as effective as standard dose in chronic myeloid leukemia: a simulation study based on phase III trial data. *Haematologica*. 2018;103(11):1825-1834.
71. Naqvi K, Jabbour E, Skinner J, et al. Early results of lower dose dasatinib (50 mg daily) as frontline therapy for newly diagnosed chronic-phase chronic myeloid leukemia. *Cancer*. 2018;124(13):2740-2747.
72. Michel C, Burchert A, Hochhaus A, et al. Imatinib dose reduction in major molecular response of chronic myeloid leukemia: results from the German Chronic Myeloid Leukemia-Study IV. *Haematologica*. 2019;104(5):955-962.
73. Saglio G, Fava C, Gale RP. Precision tyrosine kinase inhibitor dosing in chronic myeloid leukemia? *Haematologica*. 2019;104(5):862-864.
74. Chhatwal J, Mathisen M, Kantarjian H. Are high drug prices for hematologic malignancies justified? A critical analysis. *Cancer*. 2015;121(19):3372-3379.
75. Padula WV, Larson RA, Dusetzina SB, et al. Cost-effectiveness of tyrosine kinase inhibitor treatment strategies for chronic myeloid leukemia in chronic phase after generic entry of imatinib in the United States. *J Natl Cancer Inst*. 2016;108(7):
76. Shih YT, Cortes JE, Kantarjian HM. Treatment value of second-generation BCR-ABL1 tyrosine kinase inhibitors compared with imatinib to achieve treatment-free remission in patients with chronic myeloid leukaemia: a modelling study. *Lancet Haematol*. 2019;6(8):e398-e408.
77. Baccarani M, Pane F, Saglio G. Monitoring treatment of chronic myeloid leukemia. *Haematologica*. 2008;93(2):161-169.
78. 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*. 2006;108(1):28-37.
79. Branford S, Fletcher L, Cross NC, 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*. 2008;112(8):3330-3338.
80. Cross NC, White HE, Müller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia*. 2012;26(10):2172-2175.
81. Cross NC, White HE, Colomer D, et al. Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. *Leukemia*. 2015;29(5):999-1003.
82. Larsson RA. Is there a best TKI for chronic phase CML? *Blood*. 2015;126(21):2370-2375.
83. Jabbour E. Chronic myeloid leukemia: first-line drug of choice. *Am J Hematol*. 2016;91(1):59-66.
84. Gambacorti-Passerini C, Aroldi A, Cordani N, Piazza R. Chronic myeloid leukemia: Second-line drugs of choice. *Am J Hematol*. 2016;91(1):67-75.
85. Soverini S, Hochhaus A, Nicolini FE, et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. *Blood*. 2011;118(5):1208-1215.
86. Soverini S, De Benedittis C, Machova Polakova K, et al. Unraveling the complexity of tyrosine kinase inhibitor-resistant populations by ultra-deep sequencing of the BCR-ABL kinase domain. *Blood*. 2013;122(9):1634-1648.
87. Machova Polakova K, Kulvait V, Benesova A, et al. Next-generation deep sequencing improves detection of BCR-ABL1 kinase domain mutations emerging under tyrosine kinase inhibitor treatment of chronic myeloid leukemia patients in chronic phase. *J Cancer Res Clin Oncol*. 2015;141(5):887-899.
88. Soverini S, De Benedittis C, Polakova KM, et al. Next-generation sequencing for sensitive detection of BCR-ABL1 mutations relevant to tyrosine kinase inhibitor choice in imatinib-resistant patients. *Oncotarget*. 2016;7(16):21982-21990.
89. Baer C, Kern W, Koch S, et al. Ultra-deep sequencing leads to earlier and more sensitive detection of the tyrosine kinase inhibitor resistance mutation T315I in chronic myeloid leukemia. *Haematologica*. 2016;101(7):830-838.
90. Kizilers A, Crisà E, Lea N, et al. Effect of low-level BCR-ABL1 kinase domain mutations identified by next-generation sequencing in patients with chronic myeloid leukaemia: a population-based study. *Lancet Haematol*. 2019;6(5):e276-e284.
91. Abruzzese E, Trawinska MM, de Fabritiis P, Baccarani M. Management of pregnant chronic myeloid leukemia patients. *Expert Rev Hematol*. 2016;9(8):781-791.
92. Berman E, Druker BJ, Burwick R. Chronic myelogenous leukemia: pregnancy in the era of stopping tyrosine kinase inhibitor therapy. *J Clin Oncol*. 2018;36(12):1250-1256.
93. Pane F, Luciano L, Pugliese N, et al. International prospective study comparing nilotinib versus imatinib with early switch to nilotinib to obtain sustained treatment-free remission in patients with chronic myeloid leukemia. A GIMEMA and HOVON study. 60<sup>th</sup> Annual Meeting of the American Society of Hematology [abstract]. *Blood*. 2018;132(suppl 1). Abstract 1750.
94. Andrews CN, Lipton J. The true value of second-generation TKIs as first-line therapy in chronic myeloid leukaemia. *Lancet Haematol*. 2019;6(8):e385-e386.