

## ORIGINAL ARTICLE

# Determinants of frontline tyrosine kinase inhibitor choice for patients with chronic-phase chronic myeloid leukemia: A study from the Registro Italiano LMC and Campus CML

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## Abstract

**Background:** Imatinib, dasatinib, and nilotinib are tyrosine kinase inhibitors (TKIs) approved in Italy for frontline treatment of chronic-phase chronic myeloid leukemia (CP-CML). The choice of TKI is based on a combined evaluation of the patient's and the disease characteristics. The aim of this study was to analyze the use of frontline TKI therapy in an unselected cohort of Italian patients with CP-CML to correlate the choice with the patient's features.

**Methods:** A total of 1967 patients with CP-CML diagnosed between 2012 and 2019 at 36 centers throughout Italy were retrospectively evaluated; 1089 patients (55.4%) received imatinib and 878 patients (44.6%) received a second-generation (2G) TKI.

**Results:** Second-generation TKIs were chosen for most patients aged <45 years (69.2%), whereas imatinib was used in 76.7% of patients aged >65 years ( $p < .001$ ). There was a predominant use of imatinib in intermediate/high European long-term survival risk patients (60.0%/66.0% vs. 49.7% in low-risk patients) and a limited use

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of 2G-TKIs in patients with comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease, previous neoplasms, ischemic heart disease, or stroke and in those with >3 concomitant drugs. We observed a greater use of imatinib (61.1%) in patients diagnosed in 2018–2019 compared to 2012–2017 (53.2%;  $p = .002$ ). In multivariable analysis, factors correlated with imatinib use were age > 65 years, spleen size, the presence of comorbidities, and  $\geq 3$  concomitant medications.

**Conclusions:** This observational study of almost 2000 cases of CML shows that imatinib is the frontline drug of choice in 55% of Italian patients with CP-CML, with 2G-TKIs prevalently used in younger patients and in those with no concomitant clinical conditions. Introduction of the generic formulation in 2018 seems to have fostered imatinib use.

#### KEYWORDS

CML, frontline therapy, imatinib, second-generation TKI, TKI

## INTRODUCTION

Frontline treatment of chronic myeloid leukemia (CML) in chronic phase (CP) is based on tyrosine kinase inhibitors (TKIs) in virtually all patients.<sup>1</sup> At present, three TKIs have been approved for frontline treatment in Italy: imatinib and the second-generation (2G) TKIs dasatinib and nilotinib. All three drugs are highly effective in newly diagnosed CP-CML, which grants a long-term overall survival (OS) that is now approaching that of the general population.<sup>2,3</sup> Second-generation TKIs have been associated with more rapid and deeper molecular responses compared to imatinib but without significant differences in OS.<sup>4–6</sup>

None of the published guidelines and recommendations<sup>1,7,8</sup> provide indications on which TKI should be used frontline, and the choice is based on a combined evaluation of the patient's and disease characteristics, notably age, the risk of progression as defined by Sokal or European long-term survival (ELTS) scores, the presence of comorbidities, and the use of concomitant medications. The preference of the treating physician's and patient's expectations, mostly in terms of a possible TKI discontinuation and in some cases economic considerations, particularly after the advent of generic imatinib, may also play a role in TKI selection.

To date, few data are available on frontline TKI use within an entire country and on the possible drivers of treatment choice. The aim of the present work was to analyze the use of frontline TKIs in a large, unselected cohort of Italian patients diagnosed with CP-CML after the approval of dasatinib and nilotinib and to correlate patients' features to drug choice.

## MATERIALS AND METHODS

The Registro Italiano LMC (Italian CML Registry) is an initiative of the GIMEMA group to register in a dedicated web-based database (<https://www.epiclin.it/lmc>) all adult cases (aged >18 years) of CML diagnosed since 2012 at 68 hematology centers widespread throughout the entire Italian territory.<sup>9</sup> The "Campus CML" is an

active research network of more than 50 Italian physicians involved in the management of CML throughout the country, with the aim of investigating different aspects of the disease.

The present work is a retrospective analysis of 1967 patients diagnosed with CML in CP at 36 centers between January 2012 and December 2019. All participating centers were recommended to include all cases referred to them during the study period to avoid as much as possible selection biases; the number of enrolled patients reflects the estimated incidence of CML in Italy.

The clinical features recorded were age, gender, standard laboratory data, spleen size, CML risk according to Sokal and ELTS scores,<sup>10,11</sup> concomitant diseases, and concurrent medications at the time of CML diagnosis.

The study was approved by the local ethics committees at the participating centers; all patients were registered after providing informed consent.

## Statistical analysis

Continuous variables have been reported as median and interquartile range (IQR), and categorical variables have been reported as the count and relative frequency of each category. Comparisons of quantitative variables between groups of patients were performed by the Wilcoxon–Mann–Whitney test or Student *t*-test, and the association between categorical variables was tested by the Fisher exact test or  $\chi^2$  test as appropriate.

Statistical analyses were performed by using a standard statistical package (SPSS for Windows Version 25.0; Chicago, Illinois).

## RESULTS

### Baseline characteristics of the entire population

The main clinical features at diagnosis of the entire cohort are reported in Table 1. Median age at diagnosis was 59.3 years (IQR, 46.6–

**TABLE 1** Clinical features of the whole cohort and corresponding frontline TKI treatment.

	All patients (N =1967)	Frontline imatinib (n =1089)	Frontline 2G-TKI (n =878)	p
Gender, male/female, No. (%)	1140/827 (58.0/42.0)	646/443 (59.3/40.7)	493/385 (56.1/43.9)	.166
Median age (IQR), years	59.3 (46.6–71.2)	66.3 (55.2–75.4)	50.6 (40.1–62.1)	<.001
Hb (IQR), g/dL	12.6 (10.9–14.0)	12.7 (11.2–14.0)	12.4 (10.5–14.1)	.038
WBC (IQR), $\times 10^9/L$	60.1 (29.6–139.0)	52.1 (26.8–105.2)	78.7 (34.3–176.3)	<.001
PLTS (IQR), $\times 10^9/L$	354 (243–552)	343 (239–547)	363 (249–570)	.047
Spleen, No. evaluable (%)	1900	1046	854	<.001
Not palpable	1027 (54.1)	636 (60.8)	391 (45.8)	
<5 cm below costal margin	541 (28.5)	298 (28.5)	243 (28.4)	
$\geq 5$ cm below costal margin	332 (17.4)	112 (10.7)	220 (25.8)	
Sokal score, No. evaluable (%)	1880	1034	846	.056
Low	731 (38.9)	364 (35.2)	367 (43.3)	
Intermediate	863 (45.9)	522 (50.5)	341 (40.4)	
High	286 (15.2)	148 (14.3)	138 (16.3)	
ELTS score, No. evaluable (%)	1835	1007	828	<.001
Low	1044 (56.9)	519 (51.6)	525 (63.4)	
Intermediate	573 (31.2)	344 (34.1)	229 (27.6)	
High	218 (11.9)	144 (14.3)	74 (9.0)	
Arterial hypertension, No. (%)	764 (38.9)	526 (48.3)	238 (27.1)	<.001
Diabetes, No. (%)	222 (11.3)	157 (14.4)	65 (7.4)	<.001
Previous neoplasm, No. (%)	266 (13.5)	193 (17.7)	73 (8.3)	<.001
COPD, No. (%)	152 (7.7)	109 (10.0)	43 (4.9)	<.001
Ischemic heart disease, No. (%)	137 (7.7)	119 (10.9)	18 (2.0)	<.001
Cerebrovascular events, No. (%)	51 (2.6)	47 (4.3)	4 (0.4)	<.001
Other vascular diseases, No. (%)	145 (7.4)	118 (10.8)	27 (3.0)	<.001
Concomitant drugs, No. evaluable (%)	1874	1009	865	<.001
0	713 (38.0)	252 (25.0)	461 (53.3)	
1–2	511 (27.3)	270 (26.8)	241 (27.8)	
3–5	405 (21.6)	286 (28.3)	119 (13.8)	
>5	245 (13.1)	201 (19.9)	44 (5.1)	

Abbreviations: 2G-TKI, second-generation tyrosine kinase inhibitor; COPD, chronic obstructive pulmonary disease; ELTS, European long-term survival; Hb, hemoglobin; IQR, interquartile range; PLTS, platelets; WBC, white blood cell.

71.2), with 446 patients (22.7%) aged <45 years, 766 (38.9%) aged between 45 and 65 years, and 755 (38.4%) aged >65 years; 1140 patients (58.0%) were males.

Among 1881 evaluable patients, the CML risk according to the Sokal score was low in 731 patients (38.9%), intermediate in 864 (45.9%), and high in 286 (15.2%); among 1836 evaluable patients, 1044 (56.8%), 574 (31.3%), and 218 (11.9%) fell into low-, intermediate-, and high-risk categories, respectively, according to the novel ELTS score.

With regard to comorbidities, 1368 patients (69.5%) reported at least one active or previous disease at the time of CML diagnosis, the

most common being arterial hypertension ( $n = 764$ ; 38.9%), a previous neoplasm ( $n = 266$ ; 13.5%), diabetes ( $n = 222$ ; 11.3%), chronic bronchopulmonary diseases ( $n = 152$ ; 7.7%), and a history of acute myocardial infarction (AMI)/ischemic heart disease ( $n = 137$ ; 7.0%), stroke ( $n = 51$ ; 2.6%), and other vascular diseases ( $n = 145$ ; 7.4%). Among 1875 evaluable patients, 1161 (61.9%) were taking at least one concomitant medication, with 405 (21.6%) taking three to five drugs and 245 (13.1%) taking six or more drugs at the time of the TKI start.

There was a clear association between age and number of concomitant medications: among patients taking no drugs at the time

of starting the TKI, 45.8% were aged <45 years, 40.6% were aged 45–65 years, and only 13.6% were aged >65 years. For patients taking one or two concomitant medications the percentages of the three age classes were 12.5%, 48.0%, and 39.5%; in those taking three to five drugs the percentages of the three age classes were 1.8%, 32.7%, and 65.5%; and in those taking more than five drugs the percentages of the three age classes were 1.4%, 21.4%, and 77.1%, respectively.

### Characteristics according to frontline TKIs

With regard to frontline therapy, 1089 patients (55.4%) received imatinib and 878 (44.6%) were treated with a 2G-TKI: 555 patients (28.2% of the entire cohort) received nilotinib and 319 (16.2% of the entire cohort) received dasatinib; only four patients were treated frontline with bosutinib in the context of a clinical trial. The main clinical features of patients at diagnosis according to the type of frontline TKI are reported in Table 1.

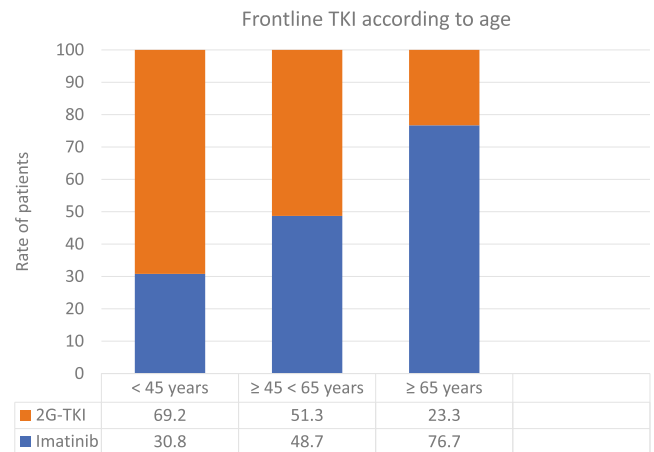
Among the 1089 patients treated frontline with imatinib, 941 (86.4%) received the standard dose (400 mg/day), whereas in 148 patients (13.6%) a reduced dose (<400 mg/day) was given. Among the 555 patients treated frontline with nilotinib, 22 (3.9%) were treated with a reduced dose (<600 mg/day), and 22 of the 319 patients (6.9%) received a reduced dose of dasatinib (<100 mg/day). Reasons for starting with a reduced dose were not available for single cases; however, the median age of patients receiving reduced doses was significantly higher than for patients starting at the standard dose: 77.5 years (IQR, 72.6–81.9) for imatinib, 74.1 years (IQR, 68.6–77.8) for dasatinib, and 53.1 years (IQR, 46.1–71.0) for nilotinib.

The main clinical features at diagnosis were evaluated by univariate analysis to find whether they played a role in the choice of frontline TKI treatment. According to age, 2G-TKIs were chosen for most patients aged <45 years (309 of 446; 69.2%), whereas imatinib was used in most patients aged >65 years (579 of 755; 76.7%) ( $p < .001$ ); among patients aged 45–65 years, the use of imatinib or a 2G-TKI was similar (Figure 1).

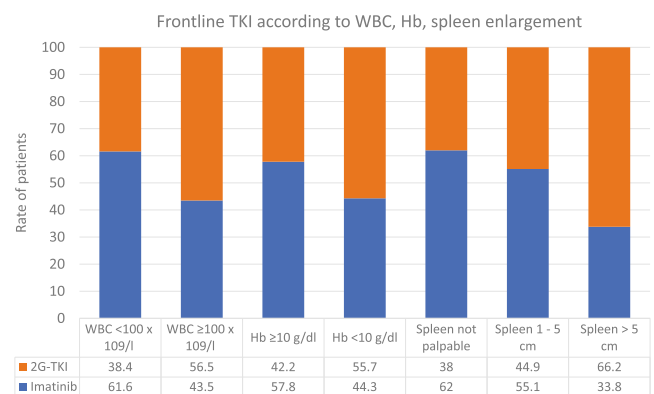
There was a predominance of imatinib use in the intermediate but not in the low and high Sokal risk scores (49.8% low, 60.5% intermediate, and 51.4% high) and in intermediate/high ELTS risk scores (49.7% low, 60.0% intermediate, and 66.0% high).

A prevalent use of 2G-TKIs was also observed in patients presenting with higher white blood cell (WBC) counts (56.5% with  $WBC \geq 100 \times 10^9/L$  vs. 38.4% with  $WBC < 100 \times 10^9/L$ ;  $p < .001$ ), lower hemoglobin (Hb) levels (55.7% with  $Hb < 10$  g/dL vs. 42.2% with  $Hb \geq 10$  g/dL;  $p = .001$ ), and a bigger spleen enlargement (66.2% with a spleen >5 cm below the costal margin vs. 44.9% with a spleen of 1–5 cm vs. 38.0% with a nonpalpable spleen;  $p < .001$ ) (Figure 2).

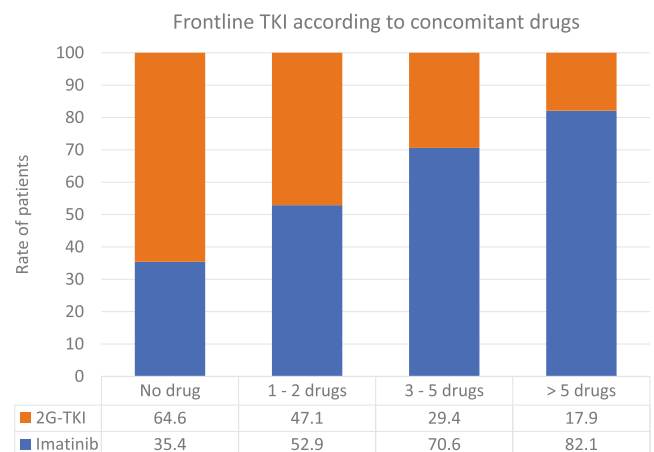
There was a decreasing use of 2G-TKIs with a higher number of concomitant drugs: 64.6% for patients not taking concomitant drugs, 47.1% with one or two drugs, 29.3% with three to five drugs, and 17.9% for more than five drugs ( $p < .001$ ) (Figure 3). Concordantly,



**FIGURE 1** Distribution of frontline TKI according to age group. 2G-TKI indicates second-generation tyrosine kinase inhibitor.



**FIGURE 2** Distribution of frontline TKI according to clinical and laboratory features. 2G-TKI indicates second-generation tyrosine kinase inhibitor; Hb, hemoglobin; WBC, white blood cell.



**FIGURE 3** Distribution of frontline TKI according to the number of concomitant medications. 2G-TKI indicates second-generation tyrosine kinase inhibitor.

there was a significantly higher use of imatinib in patients with hypertension (68.8%), diabetes (70.7%), chronic obstructive pulmonary disease (71.7%), a previous neoplasm (72.5%), and a history of AMI/

ischemic heart disease (86.8%) or stroke (92.1%) ( $p < .001$  for all conditions) (Figure 4).

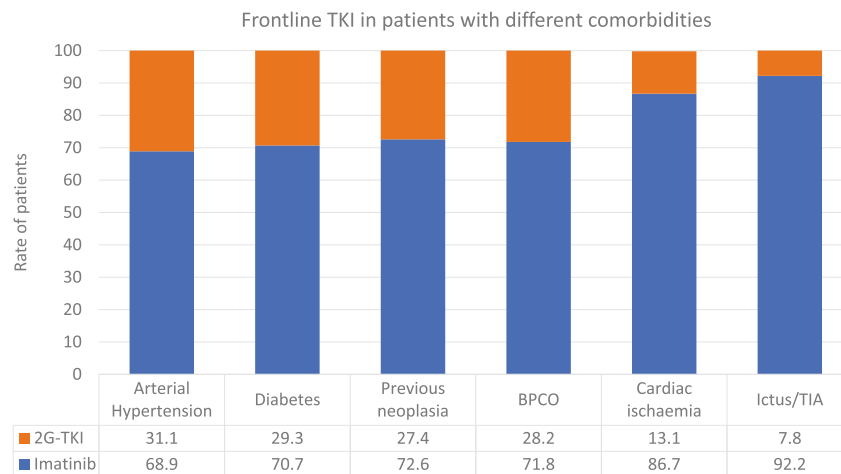
When the time frame of our analysis was divided into two periods, in accordance with the approval of generic imatinib in Italy (2017), we observed a greater use of imatinib (61.1%) in patients diagnosed in 2018–2019 compared to those of the 2012–2017 period (53.2%;  $p = .002$ ). An increment of imatinib prescription after becoming generic was observed only in patients aged  $>45$  years, whereas in patients aged  $<45$  years there was no significant difference in imatinib use between the years 2012–2017 (31.7%) and 2018–2019 (27.7%;  $p = .56$ ). In multivariable logistic regression analysis, the factors independently correlated with the choice of imatinib as frontline treatment were age  $>65$  years, spleen enlargement  $<5$  cm below the costal margin, the presence of comorbidities (second neoplasia, AMI/ischemic heart disease, and stroke), and the number of concomitant medications  $\geq 3$ , as shown in Table 2.

## DISCUSSION

With the availability of imatinib and 2G-TKIs in most countries, hematologists treating patients with CML have different options for frontline therapy, a situation sometimes referred to as an

“embarrassment of riches.” Because no clear benefit in OS has been reported by randomized clinical trials when imatinib was compared with 2G-TKIs,<sup>4–6,12</sup> possibly due to the efficacy of second-line treatment with a 2G-TKI after imatinib failure,<sup>13</sup> all published guidelines and recommendations substantially indicate any TKI as appropriate in the frontline setting. Thus, the choice is largely left to the treating clinicians, who must weigh the characteristics of the disease, the patient’s features and preferences, and sometimes also personal experience with the different TKIs and economic issues.

The major limits of the present study are its retrospective nature and the lack of decision tracking about the selection of a specific TKI for each individual patient. Nonetheless, our analysis included almost 2000 patients newly diagnosed with CML treated in many hematology units, both in academic and tertiary hospitals, widespread throughout the entire Italian territory. To the best of our knowledge, this is the largest real-life cohort in which determinants for frontline TKI choice have been addressed. Moreover, the choice of imatinib or a 2G-TKI was not biased by competing clinical trials because the only protocol active during the study period was the GIMEMA SUSTRE-NIM trial that randomized patients with CML 1:1 to frontline treatment with nilotinib or imatinib followed by a switch to nilotinib in case of a nonoptimal response.<sup>14</sup>



**FIGURE 4** Distribution of frontline TKI according to selected concomitant diseases. 2G-TKI indicates second-generation tyrosine kinase inhibitor; BPCO, bronchopulmonary chronic obstruction; TIA, transient ischemic attack.

**TABLE 2** Independent clinical features associated with the choice of frontline imatinib by multivariate logistic regression.

	Odds ratio	95% confidence interval	<i>p</i>
Age $> 65$ years	3.008	2.378–3.805	$<.001$
Spleen enlargement $< 5$ cm	2.139	1.627–2.812	$<.001$
Concomitant medications $\geq 3$	1.929	1.499–2.483	$<.001$
Previous neoplasia	1.640	1.181–2.278	.003
AMI/ischemic heart disease	2.756	1.571–4.836	$<.001$
Stroke/TIA	4.170	1.432–12.143	.009

Abbreviations: AMI, acute myocardial infarction; TIA, transient ischemic attack.

The results of this observational study demonstrate that approximately 55% of Italian patients newly diagnosed with CP-CML in the last decade received imatinib as a frontline therapy. In a retrospective French study on 507 patients diagnosed with CML between 2006 and 2016, 388 (76.5%) received imatinib and 114 (22.5%) received nilotinib or dasatinib as frontline treatment.<sup>15</sup> Similar figures emerged from the real-life study conducted between 2015 and 2017 in 257 patients treated at 21 tertiary centers and general hospitals in the United Kingdom, where imatinib was the frontline TKI in most patients (79%).<sup>16</sup> The reasons for the TKI choice were recorded for fewer than half of the patients and seemed to be a result of physicians' preference for a "standard" approach.

We found that the use of a 2G-TKI was prevalent in younger patients and in those with no concomitant clinical conditions. The former result is probably related to the higher rates of deep molecular responses (DMRs) associated with the use of 2G-TKIs compared to imatinib. In the ENESTnd study, the cumulative rate of molecular response 4.5 (MR4.5) at 5 years with nilotinib 300 mg twice daily was 54% compared to 31% with imatinib 400 mg daily.<sup>17</sup> With dasatinib 100 mg daily the cumulative 5-year MR4.5 rate was 42%, compared to 33% for imatinib 400 mg daily.<sup>5</sup> Because a DMR is a prerequisite for treatment discontinuation, the so-called treatment-free remission (TFR), it is arguable that the possibility of stopping a TKI was particularly appealing for younger patients. This has been highlighted in the survey that led to the formulation of a consensus paper from the GIMEMA CML Working Party aimed at identifying the treatment policies that could increase the possibility of a TFR.<sup>18</sup> There was a high concordance among Italian CML experts that 2G-TKIs should be preferred in all patients under the age of 40 years and in non-low risk patients aged 41–65 years, and data from the present study seem to confirm that in clinical practice these suggestions have been applied. A subanalysis among 266 Italian patients with CML enrolled in the SIMPLICITY trial reported that patients receiving frontline dasatinib ( $n = 56$ ) had a relatively high median age, approximately 62 years.<sup>19</sup> Although we do not have the exact number of patients registered in both SIMPLICITY and the present study, we can estimate that patients enrolled in both analyses represent no more than 5% of the total population we studied; the median age of dasatinib-treated patients in SIMPLICITY was higher although not directly comparable to our experience because we cumulatively reported patients treated with 2G-TKIs. Approximately 10% of our patients (192 of 1967) started TKIs at a lower dose, mostly imatinib >400 mg/day (148 of 1089; 13.6%); patients receiving low doses were elderly, which thus points to age as a major determinant in this decision.

All concomitant conditions besides CML led to a preferential use of imatinib over 2G-TKIs. The estimated impact of any examined comorbidity ranged from a rate of increased imatinib use approximately 15%–25% for arterial hypertension and diabetes (70% imatinib compared to 47% and 54% in patients without hypertension or diabetes, respectively) to over 30% for previous AMI/heart ischemic disease (86% vs. 54%) and over 40% for patients with a history of stroke (97% vs. 55%). It is well known that nilotinib has been

associated with an increased risk of peripheral arterial thrombosis and diabetes and dasatinib has been associated with different pleuropulmonary diseases,<sup>20</sup> and that the presence of comorbidities, such as arterial hypertension, may also enhance the risk of developing specific toxicities during TKI therapy. In a study from The University of Texas MD Anderson Cancer Center in 531 patients with CML treated with different TKIs, 237 patients (45%) developed cardiovascular events and, among them, hypertension was seen in 175 (74%).<sup>21</sup> A real-life Swedish study on 1238 TKI-treated patients diagnosed with CP-CML between 2002 and 2017 showed an increased incidence ratio (IRR) of morbidity compared to matched healthy controls, with a significantly higher risk in patients treated with nilotinib or dasatinib, mainly for acute myocardial infarction (IRR, 2.9 for nilotinib), chronic ischemic heart disease (IRR, 2.2 for nilotinib), pleural effusion (IRR, 11.6 for dasatinib), and upper respiratory infections (IRR, 3.0 for dasatinib).<sup>22</sup>

Quite unexpectedly, we observed a greater use of imatinib among patients with high-risk CML, although it is known that 2G-TKIs are associated with a lower rate of progression in this subset.<sup>4</sup> The counterintuitive finding of imatinib prevalence might be explained by the older age of high-risk patients because age is a parameter included in both the Sokal and ELTS scores. The number of subjects with high Sokal risk was 42 of 420 (10%) in evaluable patients aged <45 years compared to 158 of 721 (21.9%) in evaluable patients aged >65 years (21.9%), which highlights the relevance of the parameter age in the risk calculation. Among the 42 high-risk patients aged <45 years, nine received frontline imatinib and 33 received frontline 2G-TKIs. Furthermore, the increased rate of 2G-TKI use in patients with more "aggressive" features at baseline, such as bigger spleen enlargement, higher WBC counts, and lower Hb levels, points to the attention of responsible physicians to signs of high-risk disease.

Lastly, the introduction of the generic formulation in 2018 seems to have fostered the use of imatinib because no significant difference in efficacy or toxicity has been reported with the switch from the branded preparation to generic imatinib<sup>23–25</sup> with a consistent economic advantage. We feel that financial issues could have had a role in this trend, but they are coupled with increasing evidence of similar overall survival with imatinib and 2G-TKIs and with different goals of the treatment (e.g., TFR in younger patients and disease control in elderly ones).

In conclusion, the present availability of three different TKI drugs (imatinib, dasatinib, and nilotinib) makes the choice of frontline treatment of patients newly diagnosed with CML a tailored decision for each single case. In the real-life setting, this points to the physicians' judgment and to the consequent need for their continual training and comparison of data and experiences. In the present work, we have not focused on the efficacy or tolerability of the treatments because the main goal was describing possible patrons when choosing among the different TKIs available; nonetheless, given the importance of correlating present data with clinical outcomes, we are planning further analyses of this large data set of patients with CML.



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**Mario Tiribelli:** Study design, analysis, data interpretation, and writing—original draft. **Roberto Latagliata:** Study design, analysis, data interpretation, and writing—original draft. **Massimo Breccia:** Writing—review and editing. **Isabella Capodanno:** Data collection. **Maria Cristina Miggiano:** Data collection. **Francesco Cavazzini:** Data collection. **Cristina Bucelli:** Data collection. **Immacolata Attolico:** Data collection. **Sabrina Leonetti Crescenzi:** Data collection. **Sabina Russo:** Data collection. **Mario Annunziata:** Data collection. **Federica Sorà:** Data collection. **Massimiliano Bonifacio:** Data collection. **Olga Mulas:** Data collection. **Giuseppina Loglisci:** Data collection. **Alessandro Maggi:** Data collection. **Gianni Binotto:** Data collection. **Elena Crisà:** Data collection. **Anna Rita Scortechini:** Data collection. **Anna Paola Leporace:** Data collection. **Rosaria Sancetta:** Data collection. **Pamela Murgano:** Data collection. **Elisabetta Abruzzese:** Data collection. **Fabio Stagno:** Data collection. **Davide Rapezzi:** Data collection. **Debora Luzi:** Data collection. **Iolanda Vincelli:** Data collection. **Monica Bocchia:** Data collection. **Carmen Fava:** Data collection. **Alessandra Malato:** Data collection. **Monica Crugnola:** Data collection. **Michele Pizzuti:** Data collection. **Francesca Lunghi:** Data collection. **Sara Galimberti:** Data collection. **Matteo Dal-mazzo:** Data collection. **Renato Fanin:** Writing—review and editing. **Emilia Scalzulli:** Data collection. **Robin Foà:** Writing—review and editing. **Alessandra Iurlo:** Writing—review and editing. **Giuseppe Soglio:** Writing—review and editing. **Giorgina Specchia:** Writing—review and editing.

## CONFLICT OF INTEREST STATEMENT

Mario Tiribelli has been a consultant for Bristol-Myers Squibb, Incyte, and Novartis. Massimo Breccia has been an expert witness for Incyte, Pfizer, and Novartis. Cristina Bucelli has been a consultant for the Novartis Foundation for Sustainable Development. Elena Crisà has been a consultant for IRCCS Candiolo. Anna Rita Scortechini has been a consultant for 3B Medical. Anna Paola Leporace has been a consultant for Azienda Ospedaliera Sant'Andrea di Roma. Elisabetta Abruzzese has been a consultant for Istituto Científico Pfizer, Bristol-Myers Squibb, Incyte, and Novartis. Fabio Stagno has been a consultant for Novartis, Incyte, and Pfizer. Davide Rapezzi has received travel support from Novartis and Incyte. Monica Bocchia has been a consultant for Novartis and Incyte. Monica Crugnola has been a consultant for Novartis. Robin Foà has been an expert witness for Amgen and Novartis. The other authors declare no conflicts of interest.

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