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ORIGINAL ARTICLE

Chronic myeloid leukemia outcomes according to baseline risk and first-line treatment in real-world settings: Data from the Italian Network/CML Campus

Valentina Giai MD, PhD[1] | Tiziana Rosso MSc, PhD[2] | Fausto Castagnetti MD, PhD[3] | Patrizia Pregno MD[1] | Massimiliano Bonifacio MD, PhD[4] | Isabella Capodanno MD[5] | Mario Tiribelli MD, PhD[6] | Fabio Stagno MD, PhD[7] | Giovanni Caocci MD, PhD[8] | Antonella Gozzini MD[9] | Luigiana Luciano MD[10] | Sara Galimberti MD, PhD[11] | Monica Bocchia MD, PhD[12] | Andrea Patriarca MD[13] | Giuseppe Lanzarone MD[14] | Bruno Martino MD[15] | Anna Guella MD[16] | Anna Rita Scortechini MD[17] | Carmen Fava MD, PhD[18] | Claudio Fozza MD, PhD[19] | Simona Sica MD, PhD[20] | Nicola Di Renzo MD[21] | Pellegrino Musto MD, PhD[22] | Domenico Pastore MD, PhD[23] | Alessandro Maggi MD[24] | Michele Pizzuti MD[25] | Lorella Maria Antonia Melillo MD[26] | Angelo Michele Carella MD, PhD[27] | Giuseppe Tarantini MD[28] | Anna Mele MD[29] | Elisabetta Calistri MD[30] | Maria Rosaria Coppi MD[31] | Fabio Saccona MSc[2] | Emilia Scalzulli MD[32] | Beatrice Battaglio MD[4] | Miriam Iezza MD[33] | Cinzia Bitetti MD[34] | Roberto Freilone MD[1] | Gianantonio Rosti MD[35] | Francesco Albano MD, PhD[36] | Fabrizio Pane MD, PhD[37] | Giorgina Specchia MD, PhD[36] | Giovannino Ciccone MD, PhD[2] | Giuseppe Saglio MD, PhD[38] | Massimo Breccia MD[32]

Correspondence
Valentina Giai, Division of Haematology, Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino, Torino, Italy.
Email: vgiai@cittadellasalute.to.it

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Abstract

Background: Improved outcome has been reported in chronic myeloid leukemia (CML) patients treated with tyrosine kinase inhibitors (TKIs) in sponsored trials.

Methods: This is a multicenter prospective cohort study of consecutive patients with newly diagnosed chronic phase CML from 19 regions in Italy. Baseline treatments and prognostic factors on time to first optimal molecular response (≥ molecular response 3, MR3), time to disease progression, time to death from CML, and overall survival (OS) were analyzed using multivariable Fine and Gray models.

Results: The authors included 1433 CML patients: 49% (median age, 70 years) treated with frontline imatinib (IMA), and 51% treated with second-generation TKIs

(2G-TKIs; median age, 52 years). EUTOS long-term survival (ELTS) was low in 68.1% of 2G-TKIs patients, compared to 50.4% of IMA patients. Faster molecular responses were observed with 2G-TKIs within the first 6 months and maintained thereafter (subhazard ratio [sHR], 1.31; 95% confidence interval [CI], 1.15–1.50). Female gender and low ELTS risk had faster time of response. Achieving major molecular response (MMR or MR3) was associated with reduced risk of progression at 6 and 12 months. Overall, 41 patients progressed without differences between IMA and 2G-TKIs. Intermediate and high risk ELTS showed higher risk of progression and death from CML. Twenty-two CML-related deaths (16.5%) occurred mostly in the first 2 years from diagnosis, higher in 2G-TKIs patients (sHR, 1.75; 95% CI, 0.52–5.87). OS at 5 years was 88% with no clear differences between IMA and 2G-TKIs treatment after adjustment for potential confounders.

Conclusions: The study confirms faster responses with 2G-TKIs compared to IMA but similar clinical outcomes and a strong prognostic effect of ELTS.

KEYWORDS
chronic myeloid leukemia, first-line treatment, imatinib, real-life study, risk factors, second generation TKI, TKI

INTRODUCTION

Over the past 2 decades, the prognosis of chronic myeloid leukemia (CML) patients in the chronic phase has significantly improved, with overall survival (OS) rates now approaching those of the general population.[1] This remarkable progress is attributable to the availability of an extensive therapeutic armamentarium[2] and a more profound understanding of the disease's molecular mechanisms.[3] The European Leukemia Net (ELN) first introduced response milestones in 2006,[4] and their most recent update in 2020[5] has continued to guide the selection of first-line therapies and subsequent lines of treatment with tyrosine kinase inhibitors (TKIs), based on molecular response thresholds assessed at specific time points.

It is well established that patients achieving a *BCR::ABL1* transcript level of ≤10% at 3 months exhibit near-normal OS.[6] Additionally, patients reaching molecular milestones at later time points may still achieve excellent OS.[1] Conversely, those failing to meet milestones at 6 and 12 months typically receive an alternative TKI due to their worse prognosis.[7] Indeed, recent studies have shown that patients failing to meet key molecular milestones (>10% $BCR::ABL1^{IS}$ at 6 months or >1% $BCR::ABL1^{IS}$ at 12 months) have significantly lower OS at 10–12 years compared to those achieving optimal responses.[8]

However, most of the available molecular and clinical data have been derived from clinical trials, which often do not fully capture the complexity observed in real-world populations.

The aim of the present study is to evaluate outcomes based on baseline risk factors and first-line treatment in a prospective, real-world cohort of CML patients enrolled in a collaborative Italian study (CML Italian Network).

MATERIALS AND METHODS

The CML Italian Network, comprising 68 Hematology Centers across 19 Italian regions, has prospectively collected clinical and biological data for all newly diagnosed adult (≥18 years) Philadelphia (Ph) + CML patients, diagnosed from January 2013 onward. The study was approved by local ethical committees. Data were recorded in a dedicated web-based database (https://www.epiclin.it/lmc). Baseline information included sociodemographic characteristics, clinical features, and standard laboratory results. All consecutive patients who provided written informed consent were included, with no exclusion criteria. Centers enrolling at least 10 patients and with updated follow-up were included in the current analysis. Sites are listed in Table S1.

For this study, patients were stratified into two groups based on initial treatment: those receiving imatinib (IMA) and those treated with second-generation TKIs (2G-TKIs: nilotinib, dasatinib, or bosutinib).

Molecular analyses were conducted and interpreted in accordance with international guidelines. Quantitative molecular responses of $BCR::ABL1^{IS}$ were assessed using quantitative reverse transcription polymerase chain reaction performed in certified laboratories nationwide, with results expressed on the International Scale. For the purposes of this study, molecular responses achieving ≤0.1% $BCR::ABL1^{IS}$ (molecular response 3 (MR3) or better) were considered an end point for the current analyses.

Three time-to-event end points, specific to CML, were analyzed from the time of diagnosis: 1) time to first optimal molecular response (≥MR3); 2) time to disease progression; and 3) time to

death from CML, with deaths classified as CML-related if disease progression was the reason. OS, defined as the time from diagnosis to death from any cause, was also assessed across the entire cohort. Patients alive at the last follow-up were censored at that time.

CML-specific outcomes were analyzed using competing risk methods as described by Gooley.[9] In these analyses, we considered as competing events deaths from any cause for the analysis of time to first molecular response and deaths from non-CML–related causes for the analyses of time to disease progression and time to death from CML. Fine and Gray models were used to adjust comparisons for potential confounders. Additionally, Fine and Gray models were applied to evaluate the association between molecular responses at 6 and 12 months and the subsequent risk of CML progression, incorporating left truncation (landmark analysis) at the time point of the molecular assessment.

All multivariable models included a predefined set of variables capturing relevant prognostic factors at diagnosis, including age, sex, Charlson Comorbidity Index,[10] ELTS risk score, and initial treatment (IMA vs. 2G-TKI).

Statistical analyses were performed using STATA software, version 15.0.

RESULTS

Characteristics of patients

From September 2013 to April 2024, 1433 newly diagnosed CML patients were prospectively enrolled (Table 1). Patients were followed for a median of 4.2 years.

At diagnosis, 702 patients (49%) were treated with IMA, and 731 patients (51%) received 2G-TKIs: nilotinib (n = 414; 28.9%), dasatinib (n = 312; 21.8%), or bosutinib (n = 5; 0.3%). The median age was 70 years (interquartile range [IQR], 58–77) in the IMA group and 52 years (IQR, 41–63) in the 2G-TKIs group. The proportion of male patients was comparable between the two groups (59% in the IMA group and 56% in the 2G-TKIs group).

The CCI revealed significant differences between groups. In the IMA group, 538 patients (76.6%) had a CCI score of 2–3, and 154 patients (21.9%) had a score of 4–5. In contrast, among the 2G-TKIs group, 662 patients (90.6%) had a CCI score of 2–3, and 54 (7.4%) had a score of 4–5. Data were missing for 25 patients (1.7%). Across the entire cohort, the most frequent comorbidities were cardiovascular disease (n = 384; 26.8%), pulmonary disease (n = 164; 11.4%), metabolic disease (n = 126; 8.8%), and other neoplasms (n = 120; 8.4%).

According to the EUTOS long-term survival (ELTS) score, risk distribution also differed between treatment groups. Among IMA-treated patients, 354 (50.4%) were low risk, 248 patients (35.3%) were intermediate risk, and 99 patients (14.1%) were high risk. Among those receiving 2G-TKIs, 498 patients (68.1%) were low risk, 156 patients (21.3%) were intermediate risk, and 76 patients (10.4%) were high risk. Data were missing for two patients.

TABLE 1 Baseline patient characteristics by first-line treatment in the cohort of CML patients.

	First-line treatment					
	Imatinib (n = 702)		2G TKIs (n = 731)		Total (n = 1433)	
	n	%	*n*	%	*n*	%
Age groups (years)						
<30	16	2.28	55	7.52	71	4.95
31–40	26	3.70	121	16.55	147	10.26
41–50	65	9.26	172	23.53	237	16.54
51–60	96	13.68	171	23.39	267	18.63
61–70	175	24.93	155	21.20	330	23.03
71–80	225	32.05	49	6.70	274	19.12
>80	99	14.10	8	1.09	107	7.47
Sex						
Male	414	58.97	411	56.22	825	57.57
Female	288	41.03	320	43.78	608	42.43
Comorbidities						
Cardiovascular disease	273	38.89	111	15.18	384	26.80
Pulmonary disease	128	18.23	36	4.92	164	11.44
Metabolic disease	93	13.25	33	4.51	126	8.8
Other neoplasm	75	10.68	45	6.16	120	8.4
CCI						
2	420	59.83	609	83.31	1029	71.81
3	118	16.81	53	7.25	171	11.93
4	99	14.10	34	4.65	133	9.28
≥5	55	7.83	20	2.74	75	5.23
Not available	10	1.42	15	2.05	25	1.74
ELTS						
Low risk	354	50.43	498	68.13	852	59.46
Intermediate risk	248	35.33	156	21.34	404	28.19
High risk	99	14.10	76	10.40	175	12.21
Not available	1	0.14	1	0.14	2	0.14

Abbreviations: CCI, Charlson Comorbidity Index; CML, chronic myeloid leukemia; ELTS, EUTOS long-term survival; TKI, tyrosine kinase inhibitor.

Molecular response

The time to achieve at least an MR3 response was compared between TKI classes. Figure 1A shows that patients treated with 2G-TKIs achieved MR3 or better responses faster than those receiving IMA. This advantage was evident within the first 6 months and remained constant thereafter, with an adjusted subhazard ratio (sHR) of 1.31 (95% CI, 1.15–1.50) (Table 2). Among other factors analyzed, male patients exhibited a slower time to response (sHR 0.80; 95% CI, 0.71–0.90), as

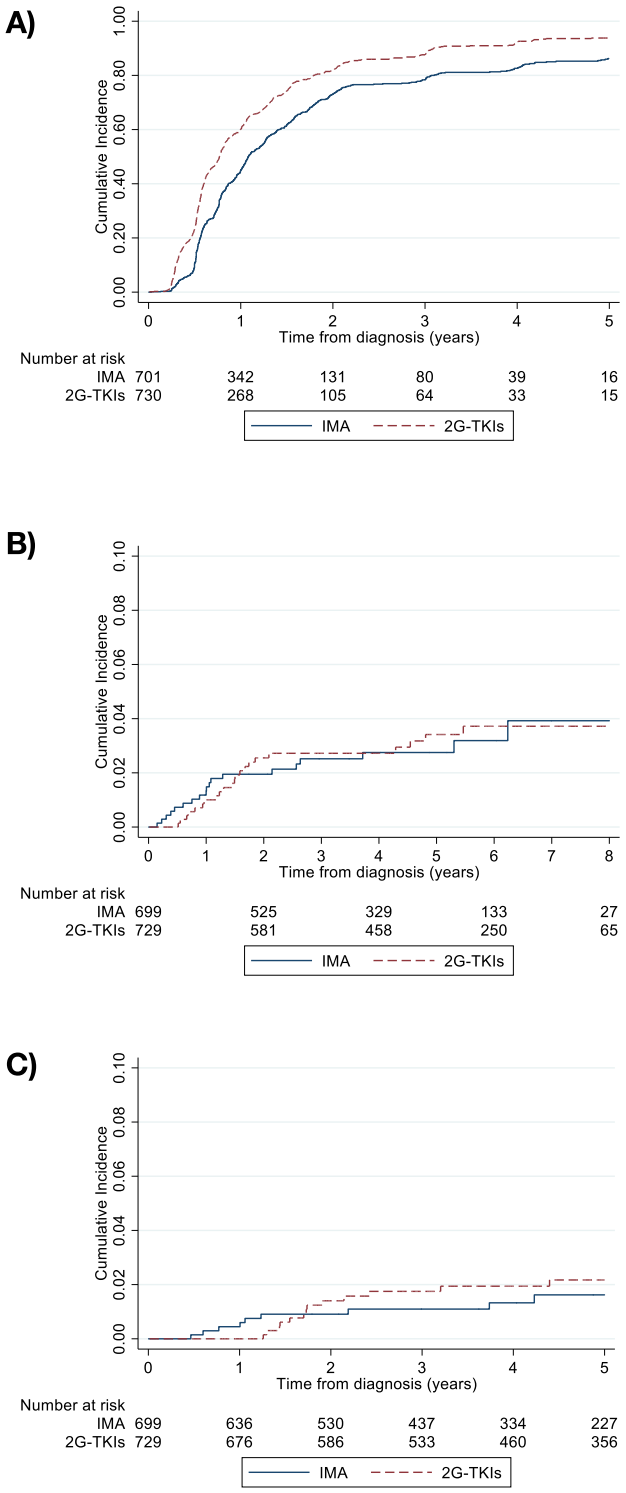

FIGURE 1 Cumulative incidence of time to molecular response (≥MR3) (A) since diagnosis of chronic myeloid leukemia (CML), estimated with the method by Gooley, considering deaths from any causes as competing events. Cumulative incidence of time to CML progression (B) and to CML-related deaths (C) since diagnosis of CML, estimated with the method by Gooley, considering the other causes of deaths as competing events.

did those with intermediate and higher ELTS scores (compared to low risk) and higher CCI. Achieving MR3 was associated with a trend of reduced risk of CML progression, both at 6 months (sHR 0.66; 95% CI, 0.26–1.70) and 12 months (sHR 0.47; 95% CI, 0.16–1.34).

Disease progression

Progression to accelerated phase (AP) or blastic phase (BP) occurred in 41 patients: 14 progressed to AP (3 deaths), and 27 progressed to BP (19 deaths). ELTS in progressed patients was low in 10 of 41 (24.4%), intermediate in 14 of 41 (34%) and high in 17 of 41 (41.5%). The cumulative incidence of progression was similar between treatment groups (Figure 1B), with a steeper slope during the first 18 months (reaching ~2%) and a slower increase thereafter (~2.5% at 4 years). No significant differences were observed between treatments (2G-TKIs vs. IMA: sHR 0.94; 95% CI, 0.40–2.21). The ELTS score remained the strongest predictor of progression risk (Table 2).

Notably, in the group of CML-related deaths (all in CP at baseline), five patients on 2G-TKIs were classified as intermediate and one patient was classified as low risk according to ELTS (Figure 2). Two of the five intermediate-risk patients underwent allogeneic bone marrow transplantation but relapsed and died; the other three patients were ineligible for transplantation and died of blastic disease as did the low-risk patient.

Nine of 22 patients who died from CML-related causes showed an ABL1 kinase domain mutation detected after disease progression, including four with T315I mutation. In addition, five of 22 patients had additional chromosomic abnormalities (ACA) at diagnosis and another seven patients had ACA at the time of progression.

Overall survival and CML-related deaths

The OS of the entire cohort is shown in Figure S1A. At 5 years, 88% (95% CI, 86–90) of patients were alive. As expected, patients treated with IMA had worse OS (Figure S1B), with a row HR (2G-TKIs vs. IMA) of 0.27 (95% CI, 0.19–0.39, $p < .0001$) and an adjusted HR of 0.77 (95% CI, 0.52–1.16, $p = .216$) (Table S2), reflecting the confounding effect due to the older median age (+18 years compared to 2G-TKIs patients) and greater comorbidity burden of IMA-treated patients (Table 1). As expected, OS of high risk ELTS patients was worse compared to intermediate and low risk patients (Figure S1C). The causes of death differed significantly between groups (Table 3). Among 133 recorded deaths at 5 years, 22 (16.5%) were CML-related: nine of 98 (9.2%) in the IMA group and 13 of 35 (37.1%) in the 2G-TKIs group (Table 3; Figure 1C). Most CML-related deaths occurred due to disease progression within the first 2 years after diagnosis ($n = 17$; 77%). Progression beyond 2 years was rare, occurring in three IMA-treated and two 2G-TKIs–treated patients (Figure 2).

TABLE 2 Effects of baseline variables on time to response (≥MR3), time to progression, and time to death from CML.

	Time to response (≥MR3)			Time to progression			Time to death from CML		
Baseline variables	**sHR[a]**	**95% CI**	***p***	**sHR[b]**	**95% CI**	***p***	**sHR[b]**	**95% CI**	***p***
Age (per year)	1.00	1.00–1.01	.825	0.98	0.95–1.00	.081	1.00	0.97–1.04	.931
Sex, M (vs. F)	0.80	0.71–0.90	<.001	1.10	0.55–2.19	.785	1.35	0.51–3.59	.542
CCI (per unit)	0.87	0.81–0.93	<.001	1.17	0.94–1.46	.151	1.18	0.89–1.56	.258
ELTS intermediate (vs. low)	0.67	0.58–0.77	<.001	3.68	1.50–9.02	.004	5.47	1.34–22.40	.018
ELTS high (vs. low)	0.51	0.42–0.62	<.001	10.63	4.64–24.37	<.001	19.20	5.10–72.26	<.001
2G-TKIs (vs. IMA)	1.31	1.15–1.50	<.001	0.94	0.40–2.21	.895	1.75	0.52–5.87	.363

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; CML, chronic myeloid leukemia; ELTS, EUTOS long-term survival; F, female; M, male; sHR, subhazard ratio; TKI, tyrosine kinase inhibitor.

[a]sHRs adjusted for all the baseline variables in the table, estimated with a Fine and Gray model, considering deaths from any cause as competing events.

[b]sHRs adjusted for all the baseline variables in the table, estimated with a Fine and Gray model, considering deaths from causes not CML-related as competing events.

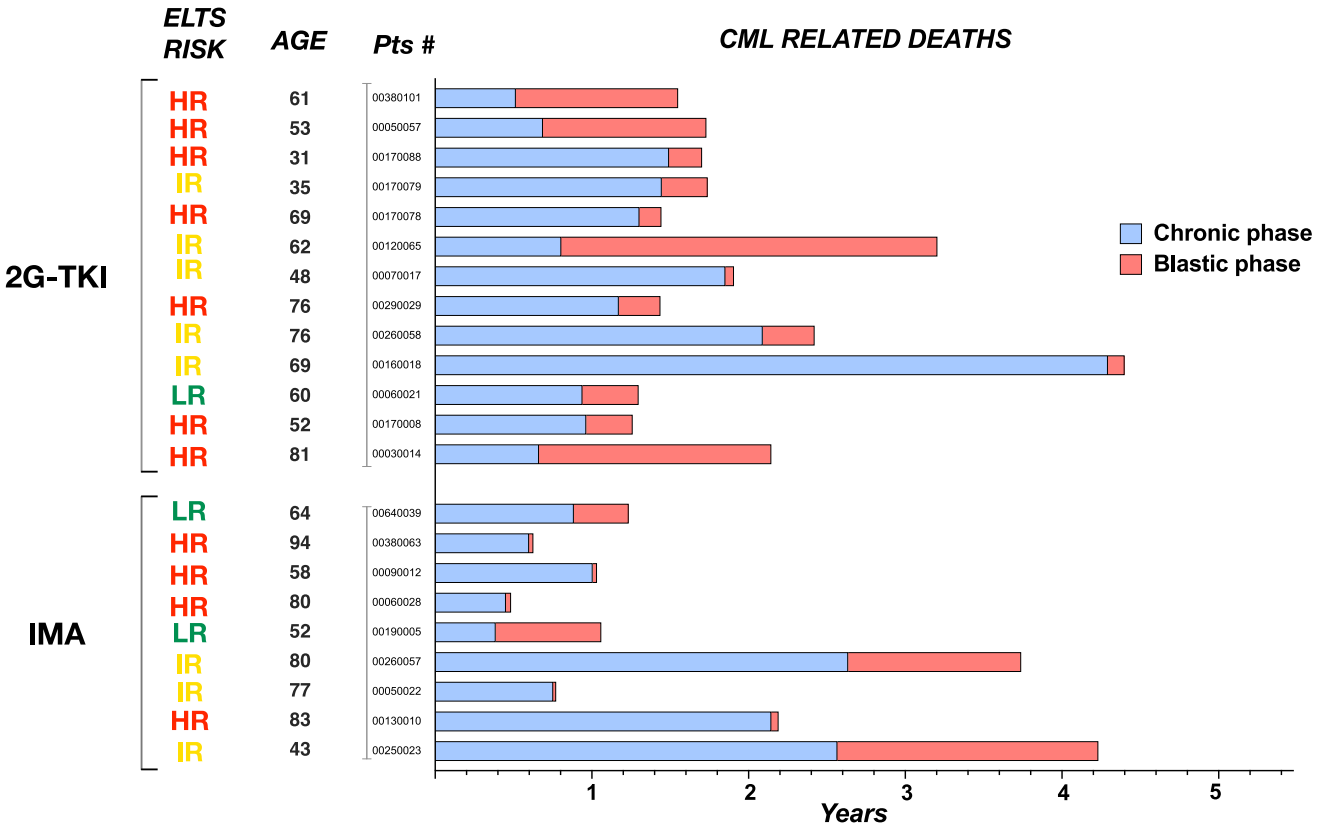

FIGURE 2 Description of the duration of the chronic and blastic phases in the 22 patients deceased from chronic myeloid leukemia, according to first-line treatment, EUTOS long-term survival (ELTS) risk, and age at diagnosis. Looking at ELTS risk, in the 2G-TKI group, seven were high risk (HR), five were intermediate risk (IR), and one was low risk (LR); in the IMA group, four were HR, three were IR, and two were LR.

The cumulative risk of CML-related deaths was slightly higher in the 2G-TKIs group (sHR 1.75); however, the small number of events introduced imprecision (95% CI, 0.52–5.87). Among the factors included in the multivariable model, the ELTS score emerged as the strongest predictor of CML-related mortality.

DISCUSSION

Currently, there are limited published data analyzing large, real-life CML cohorts, as most evidence originates from sponsored trials. In this study, we analyzed a prospective cohort of 1433 CML patients

TABLE 3 Causes of death of CML patients by first-line treatment.

	First-line treatment					
	Imatinib (n = 98)		2G TKIs (n = 35)		Total (n = 133)	
Causes of death	n	%	n	%	n	%
CML-related	9	9.2	13	37.1	22	16.5
Others	89	90.8	22	62.9	111	83.5
Cardiovascular	16	16.3	3	8.6	19	14.3
Metabolic	0	0.0	2	5.7	2	1.5
Pulmonary	7	7.1	0	0.0	7	5.3
Neoplasia	19	19.4	9	25.7	28	21.1
Bleeding	5	5.1	0	0.0	5	3.8
Nephrological	2	2.0	2	5.7	4	3.0
Infections	10	10.2	4	11.4	14	10.5
Gastrointestinal	1	1.0	0	0.0	1	0.8
Neurologic	4	4.1	0	0.0	4	3.0
Senectus	8	8.2	0	0.0	8	6.0
NA/other	17	17.3	2	5.7	19	14.3

Abbreviations: CML, chronic myeloid leukemia; NA, not available; TKI, tyrosine kinase inhibitor.

enrolled across 33 Italian hematological centers (Table S1). Consistent with previous reports, the median age at diagnosis in our cohort was 60 years.[1] Clinicians tended to select IMA for older patients, as reflected by the higher median age of 70 years in the IMA group compared to 52 years in patients treated with 2G-TKIs. This preference likely reflects IMA's well-established safety and tolerability profile,[11] making it a more suitable option for older patients with comorbidities, which were indeed more prevalent among IMA-treated patients in our study.

In terms of risk stratification, approximately 50% of IMA-treated patients were in the low-risk ELTS category, compared to 68% of patients in the 2G-TKI cohort. This discrepancy likely reflects the younger age in the latter group, as younger patients may have been preferentially treated with 2G-TKIs to facilitate deeper molecular responses and potential treatment discontinuation. These baseline differences in prognostic factors—especially age and comorbidities—strongly influence OS, necessitating a focus on specific CML-related outcomes.

As anticipated, patients treated with 2G-TKIs achieved MR3 or better responses more rapidly than those treated with IMA. This advantage was evident within the first few months of treatment and persisted throughout follow-up, with the difference remaining roughly constant. Male patients and those with higher comorbidity scores experienced slower responses. We tested the hypothesis that the lower average body weight of women might play a role, but the results of the multivariable models including weight at diagnosis did not support this explanation. In patients with older age and comorbidity, we observed a trend toward more frequent intolerance and dose reduction of TKIs (data not shown) potentially responsible for slower responses.

Achieving MR3 by 6 or 12 months was associated with a trend to lower risk of CML progression. However, interpreting these findings in terms of causality is challenging.[12] Short-term surrogate end points, such as molecular responses, may simply reflect shared baseline predictors of later clinical outcomes.

Additionally, landmark analyses, commonly employed to mitigate immortal time bias, progressively select subsets of patients at different time points, potentially introducing bias.[12]

Progression to AP or BP was strongly correlated with baseline ELTS risk. Neither patient characteristics nor initial treatment choice (2G-TKI vs. IMA) significantly influenced progression risk (sHR 0.94, p = .895). This is clinically relevant, as approximately 50% of patients who experience progression ultimately die from CML. This finding aligns with previous highlighting the ELTS score as a robust prognostic tool[13–15] but further exploration is needed to confirm these results in similar real-world populations.

The risk of CML-related death mirrored findings for disease progression, again underscoring the prognostic significance of the ELTS score (Figure 1C). Interestingly, the cumulative incidence of CML-related deaths plateaued after approximately 2 years, regardless of initial treatment. This suggests that the first 2 years of disease are critical for monitoring and managing CML-related events, especially in high-risk patients. Notably, half of all CML-related deaths (11 of 22, 50%) occurred in high-risk ELTS patients.

An interesting observation was the slightly higher risk of CML-related death in patients treated with 2G-TKIs (sHR 1.75, p = .363). This association, although imprecise due to the small number of events, may reflect a selection bias favoring 2G-TKIs in younger patients with more aggressive disease, a confounder that may not be fully controlled by the ELTS score. Additionally, it cannot be excluded that progression in 2G-TKI–treated patients may be less responsive to subsequent therapies, whereas IMA-treated patients might benefit more from second-line 2G-TKIs. This hypothesis is supported by the short time interval between progression and death observed in four of nine deceased 2G-TKI patients after progression, suggesting limited efficacy of subsequent treatments (Figure 2).

The 5-year OS for the entire cohort was 88%, consistent with prior studies.[16] As expected, younger patients in the 2G-TKI group had superior OS (94%) compared to the IMA group (81%), but this difference was heavily confounded by age and comorbidity. When compared to registrative trials of 2G-TKIs, the OS in our cohort was similar for 2G-TKI-treated patient group but inferior for IMA-treated patients, likely due to differences in age and comorbidity distributions.[17–19] These results are consistent with studies reporting similar OS in over 1500 IMA-treated patients.[16]

Of 133 total deaths, only 22 (16.5%) were CML-related deaths. The relative distribution of the other causes of death shows an excess in the IMA group for cardiovascular, pulmonary, and other age-related causes. Conversely, deaths from other neoplasms, metabolic, and neurological causes were relatively more frequent in

the 2G-TKI group. These findings underscore the importance of considering patient age, comorbidities, and causes of deaths when interpreting overall survival outcomes.

Our real-life study confirms the prognostic value of the ELTS score across all CML-related outcomes, also in a real-life context. The first 2 years of disease appear to be pivotal for prognosis and progressions occurring during this period. Beyond this time window, age and comorbidities predominantly influence survival through non-CML–related mortality.

Although 2G-TKIs and 3G-TKIs including asciminib[20] achieve faster molecular responses, this does not necessarily translate into lower progression rates or reduced CML-related mortality. The results of the ASC4FIRST trial showed an advantage of asciminib versus imatinib in the initial follow-up at 48 months, but how the drug will influence the future first line scenario remain a matter of discussion. The possibility that progression in 2G-TKI–treated patients may be less responsive to subsequent treatments warrants further investigation. Nevertheless, these findings could hold relevance especially for low- and middle-income countries.[21] This study highlights the importance of individualized treatment strategies that balance molecular response objectives with clinical outcomes, considering patient-specific factors such as age, comorbidities, and baseline ELTS risk.

AUTHOR CONTRIBUTIONS

Valentina Giai: Conceptualization, investigation, writing–original draft, validation, methodology, and visualization. **Tiziana Rosso**: Conceptualization, software, methodology, data curation, formal analysis, and validation. **Fausto Castagnetti**: Investigation, writing–review and editing, and resources. **Patrizia Pregno**: Conceptualization, investigation, methodology, visualization, supervision, and writing–review and editing. **Massimiliano Bonifacio**: Investigation, writing–review and editing, and resources. **Isabella Capodanno**: Investigation, writing–review and editing, and resources. **Mario Tiribelli**: Investigation, writing–review and editing, and resources. **Fabio Stagno**: Investigation, writing–review and editing, and resources. **Giovanni Caocci**: Investigation, writing–review and editing, and resources. **Antonella Gozzini**: Investigation, writing–review and editing, and resources. **Luigiana Luciano**: Investigation, writing–review and editing, and resources. **Sara Galimberti**: Investigation, writing–review and editing, and resources. **Monica Bocchia**: Investigation, writing–review and editing, and resources. **Andrea Patriarca**: Investigation, writing–review and editing, and resources. **Giuseppe Lanzarone**: Investigation, writing–review and editing, and resources. **Bruno Martino**: Investigation, writing–review and editing, and resources. **Anna Guella**: Investigation, writing–review and editing, and resources. **Anna Rita Scortechini**: Investigation, writing–review and editing, and resources. **Carmen Fava**: Investigation, writing–review and editing, and resources. **Claudio Fozza**: Investigation, writing–review and editing, and resources. **Simona Sica**: Investigation, writing–review and editing, and resources. **Nicola Di Renzo**: Investigation, writing–review and editing, and resources. **Pellegrino Musto**: Investigation, writing–review and editing, and resources. **Domenico Pastore**: Investigation, writing–review and editing, and resources. **Alessandro Maggi**: Investigation, writing–review and editing, and resources. **Michele Pizzuti**: Investigation, writing–review and editing, and resources. **Lorella Maria Antonia Melillo**: Investigation, writing–review and editing, and resources. **Angelo Michele Carella**: Investigation, writing–review and editing, and resources. **Giuseppe Tarantini**: Investigation, writing–review and editing, and resources. **Anna Mele**: Investigation, writing–review and editing, and resources. **Elisabetta Calistri**: Investigation, writing–review and editing, and resources. **Maria Rosaria Coppi**: Investigation, writing–review and editing, and resources. **Fabio Saccona**: Methodology, investigation, software, and data curation. **Emilia Scalzulli**: Investigation, writing–review and editing, and resources. **Beatrice Battaglio**: Investigation, writing–review and editing, and resources. **Miriam Iezza**: Investigation, writing–review and editing, and resources. **Cinzia Bitetti**: Investigation, writing–review and editing, and resources. **Roberto Freilone**: Investigation, writing–review and editing, and resources. **Gianantonio Rosti**: Investigation, writing–review and editing, and resources. **Francesco Albano**: Investigation, writing–review and editing, and resources. **Fabrizio Pane**: Investigation, writing–review and editing, and resources. **Giorgina Specchia**: Conceptualization, investigation, funding acquisition, methodology, validation, visualization, project administration, and supervision. **Giovannino Ciccone**: Conceptualization, methodology, software, formal analysis, data curation, writing–review and editing, validation, and visualization. **Giuseppe Saglio**: Conceptualization, validation, writing–review and editing, visualization, project administration, and supervision. **Massimo Breccia**: Conceptualization, investigation, writing–original draft, methodology, validation, visualization, writing–review and editing, and supervision. All the authors inserted data and discussed results, contributed to manuscript revision, and approved the submitted version.

AFFILIATIONS

[1]Division of Haematology, Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino, Torino, Italy

[2]Clinical Epidemiology Unit and CPO Piemonte, Città della Salute e della Scienza di Torino, Torino, Italy

[3]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Institute of Hematology "L. & A. Seràgnoli", Bologna, Italy

[4]Department of Medicine, Section of Hematology, University of Verona, Verona, Italy

[5]Hematology, AUSL Reggio Emilia, Reggio Emilia, Italy

[6]Division of Hematology and BMT, Azienda Ospedaliero-Universitaria di Udine, Udine, Italy

[7]Hematology Section AOU Policlinico "G. Martino", University of Messina, Messina, Italy

[8]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

[9]Hematology, University of Florence, Florence, Italy

[10]Hematology, Federico II University, Naples, Italy

[11]Section of Hematology, Oncology, Transplant and Advances in Medicine, University of Pisa, Pisa, Italy

[12]Hematology and Transplants, University of Siena, Siena, Italy

[13]Department of Translational Medicine, Universita degli Studi del Piemonte Orientale Amedeo Avogadro, Novara, Italy

[14]Division of Haematology, University of Torino, Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino, Torino, Italy

[15]Hematology Unit, Azienda Ospedaliera "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

[16]Hermatology Department, Ospedale di Trento, Trento, Italy

[17]Department of Haematology, Ospedali Riuniti di Ancona, Ancona, Italy

[18]Università Degli Studi di Torino, Dipartimento di Scienze Cliniche e Biologiche, Scienze Cliniche e Biologiche, Torino, Italy

[19]Haematology, University of Sassari, Sassari, Italy

[20]Ematologia e trapianto di cellule staminali emopoietiche, Universita Cattolica del Sacro Cuore Facolta di Medicina e Chirurgia, Rome, Italy

[21]Hematology, Vito Fazzi Hospital, Lecce, Italy

[22]Department of Precision and Regenerative Medicine and Ionian Area, "Aldo Moro" University School of Medicine, Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy

[23]Division of Hematology, Hematology and Bone Marrow Transplant Unit, Brindisi, Italy

[24]Hematology, Taranto Hospital, Taranto, Italy

[25]Hematology division, Azienda Ospedaliera San Carlo, Potenza, Italy

[26]Hematology, Ospedali Riuniti di Foggia, Foggia, Italy

[27]Hematology and Stem Cell Transplantation Unit "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo (FG), Italy

[28]Hematology, Hematology-Oncology, Barletta Hospital, Barletta, Italy

[29]Hematology Unit, Azienda C. Panico, Tricase (Le), Italy

[30]Division of Hematology, Dipartimento Medicina Clinica 1, Ospedale San Giacomo Apostolo, Treviso, Italy

[31]Hematology, Antonio Perrino Hospital, Brindisi, Italy

[32]Hematology, Department of Translational and Precision Medicine, Az. Policlinico Umberto I-Sapienza University, Rome, Italy

[33]Hematology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[34]Hematology, Presidio Ospedaliero "Madonna delle Grazie", Matera, Italy

[35]IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) "Dino Amadori", Scientific Directorate, Meldola, Italy

[36]Hematology, University of Bari, Bari, Italy

[37]CEINGE Biotecnologie Avanzate and Department of Biochemistry and Medical Biotechnology, University of Napoli Federico II, Naples, Italy

[38]Department of Clinical and Biological Sciences, University of Turin, Torino, Italy

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CONFLICT OF INTEREST STATEMENT

Valentina Giai served on advisory board for Novartis, Pfizer, and Incyte and received honoraria from Alexion, Sobi, and Roche. Massimiliano Bonifacio received honoraria from Amgen and served on advisory board for Incyte, Novartis, Bristol-Myers Squibb, and Pfizer. Elisabetta Capodanno received honoraria from Incyte, Novartis, Bristol-Myers Squibb, and Celgene and served on advisory board for Pfizer. Fabio Stagno received honoraria for Speakers Bureau from Incyte and Novartis. Sara Galimberti received honoraria for supporting meetings from Novartis, AbbVie, Pfizer, Incyte, Astra Zeneca, Jazz, Celgene, Roche, and Janssen. Andrea Patriarca received honoraria from Sobi, Novartis, Roche, Incyte, Alexion, Takeda, Pfizer, Sanofi, and Bristol-Myers Squibb. Bruno Martino received honoraria for Speakers Bureau from Incyte, Astra Zeneca, Novartis, and Janssen. Claudio Fozza received research funding from Sanofi, Amgen, Bristol-Myers Squibb, and Sobi. Pellegrino Musto received consulting fees from Beigene. Gianantonio Rosti received honoraria for Speakers Bureau from Novartis, Incyte, and Pfizer. Fabrizio Pane received fees for consulting, membership on an entity's Board of Directors or advisory committees and Speakers Bureau from Incyte, Takeda, AbbVie, Amgen, Alexion, GSK, Bristol-Myers Squibb, Janssen, Jazz, Novartis, and Pfizer. Massimo Breccia received honoraria from Novartis, Incyte, Pfizer, AbbVie, Bristol-Myers Squibb, and AOP. Giuseppe Saglio received consulting fees and Speakers Bureau from Novartis, Hikma, and Ascentage Pharma. Monica Bocchia received consulting fees from Incyte Corporation and Novartis. Fausto Castagnetti received consulting fees from Bristol-Myers Squibb, Incyte Corporation, Novartis, and Pfizer. Maria Rosaria Coppi received fees for professional activities from the American Cancer Society. Anna Guella received fees for professional activities from APSS Trento. Giuseppe Lanzarone received travel fees from AbbVie, Jazz Pharmaceuticals, and Novartis. Fabio Saccona received fees for professional activities from AOU Città della Salute e della Scienza di Torino. Anna Rita Scortechini holds a copyright for "Chronic Myeloid Leukemia Outcomes According to Baseline Risk and First-Line Treatment in Real-World." Mario Tiribelli received consulting fees from Novartis; and received fees for professional activities from Bristol-Myers Squibb and Incyte Corporation. The others declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

ORCID

Valentina Giai https://orcid.org/0009-0009-4238-1300
Massimiliano Bonifacio https://orcid.org/0000-0003-0716-1686
Mario Tiribelli https://orcid.org/0000-0001-9449-2621
Nicola Di Renzo https://orcid.org/0000-0003-0604-6934
Massimo Breccia https://orcid.org/0000-0003-1163-6162

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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