Original Article

T315I Mutation in Chronic Myeloid Leukemia: Clinicopathological Profile, Mutation Evolution, Treatment Response, and Clinical Outcomes

Manjunath S. Hiremani[1], Suresh Babu M. C[2], Mohammed Hafeez[3], Lokesh K. N[4], Rudresha A. H[5], L. K. Rajeev[5]

[1]Assistant Professor, Kidwai Memorial Institute of Oncology, Kalaburagi, Karnataka, India. [2]Director of Medical Oncology, Krishna Institute of Medical Sciences, Bengaluru, Karnataka, India. [3]Assistant Professor, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India. [4]Professor, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India. [5]Associate Professor, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India.

Abstract

Background: The T315I BCR: ABL1 kinase-domain mutation represents an important mechanism of tyrosine kinase inhibitor (TKI) resistance in chronic myeloid leukemia (CML). Its pattern of emergence and association with treatment response and clinical outcomes remain clinically relevant. **Material and Methods:** This retrospective cohort study included 34 T315I-positive patients identified from a source cohort of 101 patients with imatinib-resistant CML. Demographic, clinicopathological, prognostic, molecular, treatment-response, and outcome data were evaluated. T315I mutation patterns were categorized as isolated/upfront, upfront with additional mutation, or sequential. Complete hematological response (CHR), major molecular response (MMR), blast-phase progression, and mortality were assessed. **Results:** The mean age was 40.50 ± 13.16 years, and 91.2% were male. At diagnosis, 82.4% were in chronic phase. High-risk disease was observed in 70.6%, 61.8%, and 64.7% according to Sokal, ELTS, and EUTOS scores, respectively. Isolated/upfront T315I was observed in 79.4%, upfront T315I with an additional mutation in 5.9%, and sequential T315I in 14.7%. The median time to mutation detection was 23.5 months. CHR was achieved in 67.6%, 91.2%, and 88.2% at 3, 6, and 12 months, respectively, while only 14.7% achieved MMR. During follow-up, 29.4% progressed to blast phase and 17.6% died. Small numbers of patients with sequential and additional-mutation patterns limited definitive comparisons between mutation subgroups. **Conclusion:** T315I-positive CML was characterized by adverse prognostic features, low molecular response, and clinically important rates of blast-phase progression and mortality. Most patients had isolated/upfront T315I, while sequential and additional-mutation patterns were less frequent. Timely mutation testing and close molecular monitoring remain important for guiding individualized therapy in TKI-resistant CML.

Keywords: Chronic myeloid leukemia, T315I mutation, BCR: ABL1, tyrosine kinase inhibitor resistance, mutation evolution, molecular response, blast-phase progression.

Received: 01 September 2026 **Revised: 25 September 2026** **Accepted: 15 October 2026** **Published: 04 November 2026**

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by the Philadelphia chromosome, resulting from the reciprocal translocation t(9;22)(q34;q11) and formation of the BCR::ABL1 fusion gene. The resultant constitutively active BCR::ABL1 tyrosine kinase promotes uncontrolled proliferation, impaired apoptosis, and genomic instability of hematopoietic cells.[1,2] The introduction of tyrosine kinase inhibitors (TKIs), particularly imatinib, transformed the natural history of CML by producing durable hematological, cytogenetic, and molecular responses and substantially improving long-term survival.[3–5] Nevertheless, primary or acquired resistance to TKI therapy remains an important therapeutic challenge.

Resistance to TKIs may occur through BCR: ABL1-dependent and independent mechanisms. Among the former, BCR: ABL1 kinase-domain mutations represent one of the most clinically relevant mechanisms. These mutations can interfere with TKI binding, alter kinase conformation, and reduce drug sensitivity.[6–8] Numerous kinase-domain mutations have been described, with considerable variability in their sensitivity to different TKIs. Consequently, identification of the specific mutation is important in patients demonstrating treatment failure or loss of a previously achieved response and can influence the selection of subsequent therapy.[8–10]

Among the various BCR::ABL1 kinase-domain mutations, T315I is of particular clinical importance. The substitution of threonine by isoleucine at amino acid position 315 affects a critical residue within the ATP-binding site of BCR::ABL1. This alteration produces steric interference and eliminates a hydrogen-bond interaction required for effective binding of several TKIs.[11,12] Consequently, T315I has historically been referred to as a "gatekeeper" mutation and confers resistance to imatinib as

Address for correspondence: Dr. Manjunath S. Hiremani, Assistant Professor Kidwai Memorial Institute of Oncology, Kalaburagi, Karnataka, India.
E-mail: manjunathsh8@@gmail.com

DOI:
10.21276/amit.2026.v13.i3.1167

How to cite this article: Hiremani MS, Babu MCS, Hafeez M, Lokesh KN, Rudresha AH, Rajeev LK. T315I Mutation in Chronic Myeloid Leukemia: Clinicopathological Profile, Mutation Evolution, Treatment Response, and Clinical Outcomes. Acta Med Int. 2026:13(3):899-906.

well as several second-generation TKIs, including dasatinib, nilotinib, and bosutinib.[11–13] The development of agents with activity against T315I, particularly ponatinib and, more recently, the allosteric inhibitor asciminib, has expanded therapeutic options; however, management remains challenging, particularly in patients with advanced-phase disease or multiple prior TKI exposures.[14,15]

The biological behaviour of T315I-mutated CML is heterogeneous. The mutation may be detected as a dominant or apparently isolated mutation or may emerge during treatment following pre-existing BCR::ABL1 kinase-domain mutations. Furthermore, multiple mutations may occur within the same leukemic clone as compound mutations or may develop successively during treatment as sequential mutations.[16] Such patterns reflect clonal evolution under the selective pressure of TKI therapy and may contribute to increasingly complex resistance profiles. The distinction between isolated, sequential, and compound T315I mutations is therefore potentially important because mutation evolution may influence sensitivity to subsequent TKIs, depth of molecular response, and the risk of disease progression.

Clinical outcome following detection of T315I may also depend on the disease phase, previous treatment exposure, hematological and molecular response, and subsequent therapeutic strategy. Earlier reports have demonstrated adverse outcomes among patients harboring T315I, particularly when the mutation is detected in accelerated or blast phase.[12] However, outcomes have evolved with the availability of later-generation TKIs and improved molecular monitoring. Early identification of treatment failure and serial assessment of BCR::ABL1 transcripts and kinase-domain mutations may therefore allow timely therapeutic modification before further clonal evolution or progression occurs.

Despite the clinical importance of T315I, information describing its clinicopathological characteristics, pattern of mutation evolution, treatment response, and clinical outcomes in Indian patients remains relatively limited. Most available studies have evaluated kinase-domain mutations collectively among patients with TKI-resistant CML rather than specifically characterizing the T315I-positive population.[17,18] In particular, data comparing patients in whom T315I occurs upfront or in isolation with those in whom it develops sequentially or as part of a more complex mutation pattern are scarce. Characterizing these patterns may improve understanding of the clinical heterogeneity of T315I-mutated CML and help identify patients requiring particularly close molecular surveillance and individualized therapeutic strategies.

Therefore, the present study was undertaken to evaluate the clinicopathological profile, mutation characteristics and evolution, treatment response, disease progression, and clinical outcomes of patients with T315I-mutated CML.

Materials and Methods

This was a retrospective observational cohort study conducted in the Department of Medical Oncology at a tertiary care teaching hospital. The study evaluated patients with chronic myeloid leukemia (CML) in whom the BCR::ABL1 T315I kinase-domain mutation had been detected during evaluation for tyrosine kinase inhibitor (TKI) resistance. Clinical, hematological, cytogenetic, molecular, treatment, and follow-up information was retrieved retrospectively from institutional medical records and laboratory databases.

Study Population: The source cohort consisted of 101 patients with imatinib-resistant CML who had undergone clinical, hematological, cytogenetic, and/or molecular evaluation. For the present T315I-focused analysis, only patients in whom the T315I mutation was detected were included. A total of 34 T315I-positive patients constituted the final study population. T315I was identified in 34 of 101 (33.7%) patients in the source cohort. A prospective observational study was conducted in the Department of Medical Oncology over a period of 18 months, from January 2010 and June 2025.

Inclusion Criteria

Patients were included if they had a confirmed diagnosis of CML, had received imatinib therapy, subsequently demonstrated treatment failure or resistance, underwent BCR::ABL1 tyrosine kinase-domain mutation analysis, and were found to harbor the T315I mutation. Only patients with adequate clinicopathological, molecular, treatment-response, and follow-up information for assessment of the study outcomes were included.

Exclusion Criteria

Patients without the T315I mutation were excluded from the present analysis. Patients with incomplete treatment records, inadequate follow-up information, or insufficient laboratory and molecular data for assessment of treatment response and clinical outcomes were also excluded. Cases in which apparent treatment failure was attributable solely to documented treatment interruption or gross non-adherence without evidence supporting biological resistance were excluded wherever such information was available.

Data Collection: Relevant information was retrospectively extracted from medical records using a structured data collection format. Demographic and clinical variables included age, sex, age at diagnosis, disease phase at diagnosis, splenomegaly, duration of disease, duration of imatinib exposure, and subsequent treatment. Available hematological, cytogenetic, molecular, treatment-response, disease-progression, and final-outcome variables were recorded for each T315I-positive patient.

Hematological and Clinicopathological Assessment: Baseline hematological parameters included hemoglobin concentration, total leukocyte count, peripheral blood basophil percentage, bone marrow blast percentage, and bone marrow basophil percentage. Bone marrow examination findings were reviewed wherever available.

Patients were categorized according to the documented phase of CML as chronic phase, accelerated phase, or blast phase. Disease phase at initial diagnosis and subsequent progression during follow-up were recorded.

Prognostic Risk Assessment: Available prognostic scores were retrieved from the clinical records. Patients were categorized according to the Sokal, European Treatment and Outcome Study (EUTOS), and EUTOS Long-Term Survival (ELTS) scores. The distribution of T315I-positive patients across the respective low-, intermediate-, and high-risk categories was evaluated.

Cytogenetic Assessment: Available conventional cytogenetic

findings were reviewed for the presence of the Philadelphia chromosome [t(9;22)], variant or complex Philadelphia chromosome abnormalities, and other documented cytogenetic abnormalities. Cytogenetic information was obtained from laboratory records and evaluated in conjunction with the molecular profile.

Molecular Assessment: Molecular response was assessed using available quantitative BCR::ABL1 transcript levels, preferably reported on the International Scale. Baseline and follow-up BCR::ABL1 measurements were reviewed wherever available.

BCR::ABL1 tyrosine kinase-domain mutation analysis was reviewed to identify the T315I mutation and any additional kinase-domain mutations. The timing and pattern of mutation development were evaluated from serial molecular records.

Classification of T315I Mutation Pattern: T315I-positive patients were categorized according to the documented pattern of mutation emergence. Isolated/upfront T315I was defined as T315I detected without a previously documented kinase-domain mutation. Sequential T315I referred to T315I detected subsequently during follow-up after another BCR::ABL1 kinase-domain mutation had previously been identified. Compound/complex T315I referred to cases in which T315I was documented in association with one or more additional kinase-domain mutations according to the available molecular records.

The time to detection of the imatinib-resistance mutation was recorded and categorized as <12 months, 12–24 months, or >24 months. It was also analyzed as a continuous variable where appropriate.

Assessment of Treatment: Treatment received before and following recognition of T315I-mediated resistance was retrieved from the clinical records. Subsequent therapies included modification or switching of TKIs and other therapeutic interventions according to disease phase and clinical condition.

Treatments documented in the study records included ponatinib, dasatinib, bosutinib, asciminib, hydroxyurea, and combination approaches incorporating a TKI with chemotherapy or hypomethylating agents. Treatment selection had been determined by the treating physician according to disease phase, previous TKI exposure, mutation profile, clinical condition, and drug availability.

Assessment of Treatment Response: Treatment response was assessed from available follow-up records. Complete hematological response (CHR) was evaluated at 3, 6, and 12 months. Patients were classified according to documented achievement, non-achievement, incomplete response, or loss of CHR, as applicable.

Molecular response was assessed from serial BCR::ABL1 transcript measurements. Major molecular response (MMR) was recorded according to the molecular response documented in the clinical and laboratory records. Time to molecular response was evaluated wherever adequate serial measurements were available.

Assessment of Disease Progression and Clinical Outcomes: The principal clinical outcomes were progression to blast phase and mortality. Disease progression was determined from clinical, hematological, bone marrow, and molecular records. For patients who experienced blast-phase transformation, the available time to progression was recorded.

Final survival status was classified as alive or expired at the last available follow-up. Where adequate time-to-event information was available, follow-up duration and the interval between relevant clinical events were recorded for survival analysis.

Outcome Measures: The primary outcomes were the pattern of T315I mutation emergence, hematological and molecular treatment responses, and clinical outcomes among T315I-positive CML patients.

Secondary outcomes included clinicopathological and prognostic characteristics, timing of T315I detection, subsequent treatment received, blast-phase progression, mortality, and differences in treatment response and clinical outcomes according to isolated/upfront, sequential, and compound/complex T315I mutation patterns.

Statistical Analysis: Data were analyzed using IBM SPSS Statistics version 26.0. Continuous variables were summarized as mean ± standard deviation (SD) when approximately normally distributed and as median with interquartile range (IQR) when distributions were skewed. Categorical variables were expressed as frequencies and percentages.

Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Fisher's exact test was preferred when expected cell frequencies were small, particularly for comparisons involving sequential and compound/complex T315I mutation patterns.

Continuous variables between two groups were compared using the independent-samples t-test for normally distributed variables or the Mann–Whitney U test for non-normally distributed variables. Comparisons involving more than two mutation-pattern groups were performed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test, as appropriate.

Associations of relevant clinicopathological, molecular, treatment, and response variables with blast-phase progression and mortality were explored using univariate analyses.

All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

A total of 101 patients with imatinib-resistant chronic myeloid leukemia (CML) constituted the source cohort. The T315I mutation was identified in 34 patients, corresponding to a frequency of 33.7%. The present analysis was restricted exclusively to these 34 T315I-positive patients. The demographic, clinicopathological, molecular, treatment-response, and outcome characteristics of this T315I-positive cohort are presented below.

Demographic and Clinicopathological Characteristics

The mean age of the 34 T315I-positive patients was 40.50 ± 13.16 years, with a median age of 37.5 years (IQR: 30.5–52.3) and a range of 19–62 years. The mean age at initial diagnosis of CML was 34.85 ± 13.97 years. A marked male predominance was observed, with 31 (91.2%) males and 3 (8.8%) females. At initial diagnosis, 28 (82.4%) patients were in chronic phase, 5 (14.7%) were in accelerated phase, and 1 (2.9%) was in blast phase [Table 1].

Table 1: Demographic and baseline clinicopathological characteristics of T315I-positive CML patients (n=34)

Characteristic	Value
Age, years, mean ± SD	40.50 ± 13.16
Age, years, median (IQR)	37.5 (30.5–52.3)
Age range, years	19–62
Age at diagnosis, years, mean ± SD	34.85 ± 13.97
Age at diagnosis, median (IQR)	34.0 (24.0–45.0)
Male, n (%)	31 (91.2)
Female, n (%)	3 (8.8)
Chronic phase at diagnosis, n (%)	28 (82.4)
Accelerated phase at diagnosis, n (%)	5 (14.7)
Blast phase at diagnosis, n (%)	1 (2.9)
Total leukocyte count, $\times 10^3/\mu L$, median (IQR)	247.5 (196.3–327.5)
Hemoglobin, g/dL, mean ± SD	9.27 ± 2.10
Peripheral smear basophils, %, median (IQR)	5.5 (4.0–8.0)
Bone marrow blasts, %, median (IQR)*	3.0 (3.0–5.0)
Bone marrow basophils, %, median (IQR)	5.0 (4.0–6.0)
Baseline BCR::ABL1, %, mean ± SD	48.78 ± 21.01
Spleen size, mean ± SD	15.44 ± 3.69

The baseline hematological profile demonstrated a median total leukocyte count of 247.5 $\times 10^3/\mu L$ and mean hemoglobin concentration of 9.27 ± 2.10 g/dL. Median peripheral smear basophils were 5.5%, while median bone marrow blasts and basophils were 3.0% and 5.0%, respectively. The mean baseline BCR::ABL1 transcript level was 48.78 ± 21.01%, indicating a substantial molecular disease burden in the study population [Table 1].

Prognostic Risk Profile: A large proportion of T315I-positive patients belonged to adverse prognostic categories. According to the Sokal score, 24 (70.6%) patients were high-risk, 9 (26.5%) were intermediate-risk, and only 1 (2.9%) was low-risk. Similarly, 21 (61.8%) patients were classified as high-risk and 13 (38.2%) as intermediate-risk according to ELTS, with no patients in the low-risk category. The EUTOS score classified 22 (64.7%) patients as high-risk and 12 (35.3%) as low-risk [Table 2].

Table 2: Prognostic risk profile of T315I-positive CML patients (n=34)

Prognostic parameter	n (%) / Value
Sokal score, mean ± SD	1.58 ± 0.48
Sokal low risk	1 (2.9)
Sokal intermediate risk	9 (26.5)
Sokal high risk	24 (70.6)
ELTS score, mean ± SD	2.50 ± 0.72
ELTS low risk	0 (0.0)
ELTS intermediate risk	13 (38.2)
ELTS high risk	21 (61.8)
EUTOS score, mean ± SD	105.65 ± 28.33
EUTOS low risk	12 (35.3)
EUTOS high risk	22 (64.7)

Thus, high-risk disease was common among T315I-positive patients irrespective of the prognostic system employed. More than two-thirds were high-risk by Sokal criteria, while approximately three-fifths were classified as high-risk by both ELTS and EUTOS systems [Table 2].

Pattern and Timing of T315I Mutation

Among the 34 T315I-positive patients, 29 (85.3%) had T315I detected upfront/concurrently, whereas 5 (14.7%) demonstrated sequential emergence of T315I after a previously documented BCR::ABL1 kinase-domain mutation. On detailed classification, 27 (79.4%) had isolated/upfront T315I, 2 (5.9%) had upfront T315I with an additional mutation, and 5 (14.7%) had sequential T315I [Table 3].

Table 3: Pattern and timing of T315I mutation among T315I-positive patients (n=34)

Mutation characteristic	n (%) / Value
Upfront/concurrent T315I	29 (85.3)
Sequential T315I	5 (14.7)
Isolated/upfront T315I	27 (79.4)
Upfront T315I with additional mutation	2 (5.9)
Sequential emergence of T315I	5 (14.7)
Time to mutation detection, months, median (IQR)	23.5 (13.3–83.5)
Range, months	4–204
Mutation detected <12 months	8 (23.5)
Mutation detected at 12–24 months	10 (29.4)
Mutation detected >24 months	16 (47.1)

The median time to detection of the resistance mutation was 23.5 months (IQR: 13.3–83.5), with a wide range of 4–204 months. Eight (23.5%) patients had mutation detection within 12 months, 10 (29.4%) between 12 and 24 months, and 16 (47.1%) after more than 24 months of therapy. Thus, nearly half of the T315I-positive patients demonstrated late detection beyond 24 months [Table 3].

Hematological and Molecular Treatment Response: At 3 months, complete hematological response (CHR) was achieved in 23 (67.6%) patients, while 10 (29.4%) had no CHR and 1 (2.9%) had an incomplete CHR. By 6 months, CHR was documented in 31 (91.2%) patients. At 12 months, 30 (88.2%) patients had CHR, while 2 (5.9%) had no CHR and 2 (5.9%) had lost a previously achieved CHR [Table 4].

Table 4: Hematological and molecular treatment response among T315I-positive patients (n=34)

Treatment response	n (%)
CHR at 3 months	23 (67.6)
Incomplete CHR at 3 months	1 (2.9)
No CHR at 3 months	10 (29.4)
CHR at 6 months	31 (91.2)
No CHR at 6 months	2 (5.9)
Loss of CHR at 6 months	1 (2.9)
CHR at 12 months	30 (88.2)
No CHR at 12 months	2 (5.9)
Loss of CHR at 12 months	2 (5.9)
MMR achieved	5 (14.7)
MMR not achieved	29 (85.3)
Time to MMR among responders, months, median (IQR)	14.0 (12.0–18.0)

Despite relatively high hematological response rates at 6 and 12 months, molecular response was considerably less frequent. Major molecular response (MMR) was achieved in only 5 (14.7%) patients, while 29 (85.3%) did not achieve MMR. Among the five patients who achieved MMR, the median time to MMR was 14 months (IQR: 12–18 months) [Table 4].

Treatment Profile: Treatment exposure following resistance and mutation detection was heterogeneous. Hydroxyurea was documented in 13 (38.2%) patients and ponatinib in 12 (35.3%). Five (14.7%) patients received a hypomethylating agent in combination with a TKI, while 3 (8.8%) each received BFM-based therapy with a TKI and dasatinib. Bosutinib, asciminib, imatinib 600 mg, and low-dose cytarabine (LDAC) with a TKI were each documented in one patient [Table 5].

Table 5: Treatment profile of T315I-positive CML patients (n=34)

Treatment	n (%)
Hydroxyurea	13 (38.2)
Ponatinib	12 (35.3)
Hypomethylating agent + TKI	5 (14.7)
BFM-based therapy + TKI	3 (8.8)
Dasatinib	3 (8.8)
LDAC + TKI	1 (2.9)
Imatinib 600 mg	1 (2.9)
Bosutinib	1 (2.9)
Asciminib	1 (2.9)

The treatment pattern demonstrated substantial heterogeneity, reflecting multiple lines of therapy and changes in treatment during the disease course. Ponatinib was documented in approximately one-third of patients, whereas hydroxyurea was the most frequently recorded treatment exposure among the listed treatment variables [Table 5].

Disease Progression and Final Clinical Outcomes: During follow-up, 10 (29.4%) of the 34 T315I-positive patients progressed to blast phase, whereas 24 (70.6%) did not. Among the 10 patients who progressed, the median recorded time to progression was 34 months (IQR: 20.5–80.8 months). At final assessment, 28 (82.4%) patients were alive and 6 (17.6%) had died [Table 6].

Table 6: Disease progression and final clinical outcomes among T315I-positive patients (n=34)

Clinical outcome	n (%) / Value
Progression to blast phase	10 (29.4)
No progression to blast phase	24 (70.6)
Time to progression among progressors, months, median (IQR)	34.0 (20.5–80.8)
Alive at final assessment	28 (82.4)
Expired	6 (17.6)

These findings demonstrated that nearly one-third of T315I-positive patients experienced blast-phase progression during the available follow-up. Although the majority remained alive at final assessment, mortality occurred in

approximately one-sixth of the cohort [Table 6].

Treatment Response and Outcomes According to T315I Mutation Pattern: To explore whether the mode of T315I emergence was associated with clinical behavior, patients were categorized as isolated/upfront T315I (n=27), upfront T315I with an additional mutation (n=2), or sequential T315I (n=5). The response and outcome distributions according to these mutation patterns are presented in [Table 7].

Table 7: Treatment response and clinical outcomes according to T315I mutation pattern

Outcome	Isolated/upfront T315I (n=27)	Upfront T315I + additional mutation (n=2)	Sequential T315I (n=5)
CHR at 3 months	19 (70.4)	1 (50.0)	3 (60.0)
CHR at 6 months	25 (92.6)	1 (50.0)	5 (100.0)
CHR at 12 months	23 (85.2)	2 (100.0)	5 (100.0)
MMR achieved	4 (14.8)	0 (0.0)	1 (20.0)
Progression to blast phase	8 (29.6)	1 (50.0)	1 (20.0)
Mortality	4 (14.8)	1 (50.0)	1 (20.0)
Alive at final assessment	23 (85.2)	1 (50.0)	4 (80.0)

Values are n (%).

Among patients with isolated/upfront T315I, CHR was achieved in 70.4% at 3 months, 92.6% at 6 months, and 85.2% at 12 months. MMR was achieved in 14.8%, while 29.6% progressed to blast phase and 14.8% died. Among the five patients with sequential T315I, 60.0% achieved CHR at 3 months and all achieved CHR at 6 and 12 months; one patient (20.0%) achieved MMR, one (20.0%) progressed to blast phase, and one (20.0%) died. Of the two patients with upfront T315I accompanied by an additional mutation, one progressed to blast phase and died [Table 7].

Discussion

The present study specifically evaluated the clinicopathological profile, pattern of mutation evolution, treatment response, and clinical outcomes among 34 patients with T315I-mutated chronic myeloid leukemia (CML). Unlike the parent cohort, which included all patients with imatinib-resistant CML, the present analysis focused exclusively on T315I-positive patients, thereby allowing a more detailed assessment of this clinically important gatekeeper mutation. The major findings were a predominance of younger male patients, a high proportion of adverse prognostic risk categories, predominantly isolated/upfront occurrence of T315I, relatively low achievement of major molecular response (MMR), and clinically important rates of blast-phase progression and mortality.The mean age of the T315I-positive patients was 40.50 ± 13.16 years, while the mean age at diagnosis was 34.85 ± 13.97 years. Males constituted 91.2% of the study population. At initial diagnosis, 82.4% of patients were in chronic phase, 14.7% in accelerated phase, and 2.9% in blast phase. The relatively young age of the study population was consistent with the pattern reported in Indian CML cohorts, where patients generally present at a younger age than those described in Western populations. The predominance of chronic-phase disease at initial presentation also indicates that development of T315I was not restricted to patients initially presenting with advanced disease. A notable observation was the high baseline prognostic risk burden among T315I-positive patients. High-risk disease was identified in 70.6% according to Sokal, 61.8% according to ELTS, and 64.7% according to EUTOS criteria. This suggests that a considerable proportion of patients who subsequently harbored T315I already had adverse disease characteristics. Previous studies have demonstrated an association between kinase-domain mutations and advanced or resistant disease, with T315I being particularly relevant because of its resistance profile.[7,12] However, because the present analysis included only T315I-positive patients and did not use T315I-negative patients as a comparator, these findings should be interpreted as characterization of the T315I population rather than evidence that high-risk scores independently predicted T315I development. The T315I mutation accounted for 34 of 101 (33.7%) patients in the original imatinib-resistant cohort. This finding is comparable with Rajappa et al,[15] who detected kinase-domain mutations in 29 of 90 imatinib-resistant patients, with T315I being the most frequent mutation, occurring in 9 of 29 mutation-positive patients (31.0%). Majumdar et al,[16] in a large Indian series of 791 patients with TKI intolerance or resistance, detected BCR::ABL1 kinase-domain variants in 236 patients (29.8%), with T315I among the most frequently identified variants. Other Indian data have likewise identified T315I as one of the predominant kinase-domain abnormalities in TKI-resistant CML.[7] These observations support the clinical importance of specifically identifying T315I during evaluation of patients with inadequate or lost response to TKI therapy. An important aspect of the present study was the characterization of the pattern of T315I emergence. Of the 34 patients, 27 (79.4%) had isolated/upfront T315I, 2 (5.9%) had upfront T315I with an additional mutation, and 5 (14.7%) demonstrated sequential emergence of T315I. The median time to detection of the resistance mutation was 23.5 months, with 47.1% being detected after more than 24 months. These findings illustrate the dynamic nature of BCR::ABL1 kinase-domain evolution during treatment. Sequential acquisition of mutations may result from the selective pressure exerted by successive TKIs, allowing resistant subclones to expand over time.[9,11] Majumdar et al,[16] reported compound mutations in 33 of 236 (13.3%) mutation-positive patients, further demonstrating that multiple kinase-domain abnormalities are not uncommon in heavily treated or resistant CML. The distinction between isolated, sequential, and multiple/compound mutations is clinically relevant because accumulation of kinase-domain abnormalities may further restrict therapeutic options. Shah et al,[11] demonstrated that multiple BCR::ABL1 kinase-domain mutations may emerge during sequential TKI therapy and contribute to increasingly complex patterns of resistance. In the present cohort, however,

the number of patients with additional or sequential mutations was small. Therefore, the observed differences between mutation patterns should be considered exploratory rather than evidence of an independent prognostic effect.

Hematological response improved over time in the present cohort. CHR was achieved in 67.6% of patients at 3 months, increasing to 91.2% at 6 months and remaining high at 88.2% at 12 months. In contrast, only 5 patients (14.7%) achieved MMR, indicating that restoration or maintenance of hematological control did not necessarily translate into a deep molecular response. Rajappa et al,[15] reported CHR in 55.5% and major cytogenetic response in 39% of imatinib-resistant patients following imatinib dose escalation. The relatively low MMR rate in our T315I-positive population is clinically important because T315I interferes with the activity of imatinib and several second-generation TKIs.[12–14] Consequently, hematological response alone may underestimate the persistence of resistant molecular disease. Treatment following detection of resistant disease was heterogeneous, reflecting the retrospective nature of the cohort, different treatment periods, disease phases, previous TKI exposure, and availability of subsequent therapies. Ponatinib was documented in 35.3% of patients, while hydroxyurea was recorded in 38.2%. Smaller proportions received dasatinib, bosutinib, asciminib, hypomethylating agents with TKIs, or chemotherapy-based combinations. This treatment heterogeneity is relevant when interpreting outcomes because patients did not receive a uniform post-T315I therapeutic strategy. T315I has historically represented a major therapeutic challenge because the mutation confers resistance to imatinib and several second-generation TKIs, making mutation-directed treatment particularly important.[13,14] Disease progression remained an important adverse outcome. Ten of the 34 T315I-positive patients (29.4%) progressed to blast phase, with a median time to progression of 34 months among those who progressed. At final assessment, 28 patients (82.4%) were alive, while 6 (17.6%) had died. These observations are consistent with previous evidence indicating that T315I can be associated with adverse clinical outcomes, although prognosis is strongly influenced by disease phase at the time of mutation detection. Nicolini et al,[12] demonstrated impaired survival associated with T315I among TKI-resistant chronic-phase CML patients. Similarly, earlier work examining patients with T315I after imatinib failure showed that survival was strongly dependent on disease stage, with substantially better outcomes among patients remaining in chronic phase than among those with advanced disease. The present study also explored outcomes according to the pattern of T315I evolution. Among the 27 patients with isolated/upfront T315I, 8 (29.6%) progressed to blast phase and 4 (14.8%) died. Among the five patients with sequential T315I, one (20.0%) progressed and one (20.0%) died. Of the two patients with upfront T315I accompanied by another mutation, one progressed and died. MMR was achieved in 14.8% of isolated/upfront cases, none of the two additional-mutation cases, and 20.0% of sequential cases. Although the proportion of adverse outcomes appeared high in the very small additional-mutation subgroup, meaningful statistical comparison was limited by the subgroup sizes. These findings therefore do not establish that one pattern of T315I evolution was prognostically worse than another. The mutation-evolution findings should also be interpreted in the context of clonal selection during TKI treatment. Kinase-domain mutations may be detectable before overt clinical deterioration and may expand under continued therapeutic selection.[10] Branford et al,[10] demonstrated that detection of BCR::ABL1 kinase-domain mutations could identify patients at increased risk of subsequent disease progression. Similarly, mutations including T315I have been reported more frequently in advanced-phase disease and during progression from chronic to accelerated or blast phase.[6] These observations emphasize the importance of timely mutation analysis when treatment failure or loss of response is identified. Our findings are also supported by more recent Indian experience. Majumdar et al,[16] demonstrated considerable molecular heterogeneity among TKI-resistant/intolerant patients, including compound mutations, and reported poor survival among the limited number of T315I-positive patients with available follow-up. More recent Indian data have similarly identified T315I as a frequent mutation among patients with frontline TKI resistance and reported inferior overall survival among patients harboring T315I or ATP-binding-region mutations. Collectively, these observations reinforce the clinical relevance of T315I testing, while also demonstrating that outcomes are influenced by disease phase, clonal evolution, response to subsequent therapy, and availability of mutation-directed treatment.

Conclusion

The present study demonstrated that T315I-mutated CML was characterized by a high proportion of adverse prognostic risk profiles and predominantly occurred as an isolated/upfront mutation (79.4%). Although complete hematological response improved from 67.6% at 3 months to 88.2% at 12 months, only 14.7% of patients achieved major molecular response. During follow-up, 29.4% of patients progressed to blast phase and 17.6% died. Sequential and additional-mutation patterns were less frequent, and their small numbers limited definitive comparison of outcomes between mutation patterns. These findings highlight the clinical significance of T315I and emphasize timely mutation testing, close molecular monitoring, and individualized mutation-directed therapy in TKI-resistant CML.

Limitation: The present study had certain limitations. Its retrospective and single-center design and the relatively small T315I-positive sample size limited the statistical power for subgroup comparisons. In particular, only five patients had sequential T315I and two had upfront T315I with additional mutations; therefore, definitive conclusions regarding differences in outcomes according to mutation evolution could not be drawn. Treatment after T315I detection was heterogeneous, and the study covered patients receiving different subsequent therapeutic approaches. Furthermore, the available molecular data did not necessarily permit clonal phasing of all coexisting mutations; therefore, cases with additional mutations should be interpreted cautiously when applying the strict molecular definition of a compound mutation.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Bansal S, Prabhash K, Parikh P. Chronic myeloid leukemia data from India. Indian J Med Paediatr Oncol. 2013;34(3):154-158.
2. Ganesan P, Kumar L. Chronic myeloid leukemia in India. J Glob Oncol. 2017;3(1):64-71.
3. Cohen MH, Williams G, Johnson JR, Duan J, Gobburu J, Rahman A, et al. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. Clin Cancer Res. 2002;8(5):935-942.
4. Roy L, Guilhot J, Krahnke T, Guerci-Bresler A, Druker BJ, Larson RA, et al. Survival advantage from imatinib compared with the combination interferon-α plus cytarabine in chronic-phase chronic myelogenous leukemia: historical comparison between two phase 3 trials. Blood. 2006;108(5):1478-1484.
5. Kantarjian H, O'Brien S, Jabbour E, Garcia-Manero G, Quintas-Cardama A, Shan J, et al. Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience. Blood. 2012;119(9):1981-1987.
6. Hochhaus A, Kreil S, Corbin AS, La Rosée P, Müller MC, Lahaye T, et al. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. Leukemia. 2002;16(11):2190-2196.
7. Jabbour E, Kantarjian H, Jones D, Talpaz M, Bekele N, O'Brien S, et al. Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate. Leukemia. 2006;20(10):1767-1773.
8. Alves R, Gonçalves AC, Rutella S, Almeida AM, De Las Rivas J, Trougakos IP, et al. Resistance to tyrosine kinase inhibitors in chronic myeloid leukemia—from molecular mechanisms to clinical relevance. Cancers (Basel). 2021;13(19):4820.
9. Von Bubnoff N, Schneller F, Peschel C, Duyster J. BCR-ABL gene mutations in relation to clinical resistance of Philadelphia-chromosome-positive leukaemia to STI571: a prospective study. Lancet. 2002;359(9305):487-491.
10. Branford S, Rudzki Z, Walsh S, Grigg A, Arthur C, Taylor K, et al. High frequency of point mutations clustered within the adenosine triphosphate-binding region of BCR/ABL in patients with chronic myeloid leukemia or Ph-positive acute lymphoblastic leukemia who develop imatinib (STI571) resistance. Blood. 2002;99(9):3472-3475.
11. Shah NP, Nicoll JM, Nagar B, Gorre ME, Paquette RL, Kuriyan J, et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell. 2002;2(2):117-125.
12. Nicolini FE, Ibrahim AR, Soverini S, Martinelli G, Müller MC, Hochhaus A, et al. The BCR-ABL T315I mutation compromises survival in chronic phase chronic myelogenous leukemia patients resistant to tyrosine kinase inhibitors, in a matched pair analysis. Haematologica. 2013;98(10):1510-1516.
13. O'Hare T, Eide CA, Deininger MW. Bcr-Abl kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. Blood. 2007;110(7):2242-2249.
14. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009;27(3):469-471.
15. Rajappa S, Mallavarapu KM, Gundeti S, Paul TR, Jacob RT, Digumarti R, et al. Kinase domain mutations and responses to dose escalation in chronic myeloid leukemia resistant to standard dose imatinib mesylate. Indian J Med Paediatr Oncol. 2013 Jul;34(3):221-3.
16. Majumdar A, Katara R, Mishra A, Gupta A, Sharma DK, Srivastava AK, et al. A retrospective analysis of BCR-ABL1 kinase domain mutations in the frontline drug intolerant or resistant chronic myeloid leukemia patients: an Indian experience from a high-end referral laboratory. South Asian J Cancer. 2024;13(2):132-141.