The silent players: Atypical *BCR-ABL* isoforms as biomarkers and therapeutic hurdles in CML pathogenesis (Review)

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Abstract. Chronic myeloid leukemia (CML) is a hematological malignancy driven by diverse genetic aberrations, with the Philadelphia chromosome and its resultant *BCR-ABL1* fusion gene constituting key pathogenic drivers. Atypical *BCR-ABL1* fusion transcripts have distinctive structural and functional properties. Structural divergence in these variants leads to functional alterations of encoded oncoproteins, potentially influencing disease progression and therapeutic responsiveness. Conventional diagnostic modalities, including reverse transcription-PCR and fluorescence in situ hybridization, may fail to detect rare variants, necessitating complementary high-sensitivity techniques such as next-generation sequencing). Tyrosine kinase inhibitors (TKIs), including imatinib and dasatinib, remain cornerstone treatments; however, marked inter-variant heterogeneity in TKI responsiveness is observed: Patients harboring *e13a3*/*e14a3* transcripts generally show favorable prognoses, while those with *e1a3*/*e6a2* variants demonstrate an increased risk of relapse and/or TKI resistance, often requiring multimodal strategies combining chemotherapy or allogeneic hematopoietic stem cell transplantation. Although Chimeric Antigen Receptor)-T cell therapy has shown promise in treating (Philadelphia chromosome-positive B-cell Acute Lymphoblastic Leukemia, its application in CML, particularly in variants such as *e1a3* or *e6a2*, is not currently recommended as a first-line treatment. Despite advances in elucidating the clinical implications of fusion gene heterogeneity in leukemogenesis, the prognostic value of atypical *BCR-ABL1* isoforms requires further validation through multicenter studies with extended cohorts. This review aimed to summarize cases of atypical fusion genes in CML, with analysis of clinical characteristics, therapeutic interventions, and prognostic outcomes, to provide clinicians with enhanced reference material for improved patient management.

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1. Introduction

Chronic myeloid leukemia (CML) is a life-threatening hematological malignancy driven by intricate and multifactorial pathogenic mechanisms that underlie its clinical heterogeneity and therapeutic challenges. The Philadelphia chromosome (Ph), arising from a reciprocal translocation t(9;22)(q34;q11.2), is detected in up to 95% of adult CML cases (1). This chromosomal aberration generates an abnormal *BCR-ABL1* fusion transcript, with molecular detection of this transcript serving as a key component for genetic confirmation of CML diagnosis (2,3). Recent advancements in molecular biology have highlighted the emerging role of atypical fusion genes in CML pathogenesis and progression (4,5). In Ph-positive leukemia, the canonical *BCR-ABL1* fusion gene functions as a pivotal oncogenic driver. Variable chromosomal breakpoints within *BCR* and *ABL1* genes result in distinct *BCR-ABL1* transcript variants and corresponding protein isoforms (6). The *e13a2* and *e14a2* subtypes represent the most prevalent *BCR-ABL1* isoforms in patients with CML, both containing intact sequences encoding the Src homology 3 domain(SH3), SH2 and kinase domains of *ABL1*. Beyond these common variants,

rare fusion genotypes including *e13a3*, *e14a3* and *e1a3* have been documented (7,8). The *e13a3* and *e14a3* subtypes, characterized by the absence of *ABL1* exon 2, collectively account for <1% of CML cases (9). These atypical fusion proteins exhibit structural and functional alterations secondary to *ABL1* truncation, potentially influencing leukemia biological behavior, therapeutic responsiveness and clinical outcomes. Recent study has revealed that these atypical variants may regulate cellular signaling pathways and gene expression, influencing the progression of leukemia (3,4). Simvastatin overcomes drug resistance in chronic myeloid leukemia cells to imatinib by inhibiting the PI3K/AKT survival signaling pathway and downregulating its controlled anti-apoptotic proteins (10). Simultaneously, in combination with imatinib, it interferes with Wnt/β-catenin signaling and increases suppressive histone modification to decrease expression of the oncogene. Through these multi-pathway effects, it ultimately induces mitochondrial pathway apoptosis, thereby effectively overcoming imatinib resistance (10). Furthermore, emerging targeted therapies for these atypical variants are under investigation, aiming to improve patient outcomes and overcome the limitations of current treatment strategies (11). Multicenter studies, including the European Treatment Outcome Study (EUTOS) collaborative network, are advancing understanding of atypical *BCR-ABL1* fusion genes in CML (4,12). These studies have developed protocols for monitoring these variants using advanced techniques, such as reverse transcription-quantitative (RT-q)PCR, as standard methods are not applicable because its 'standardized' or 'universal' detection tools (primers and probes) are designed for 'typical' or 'common' fusion variants. When atypical variants are encountered, these tools cannot bind and recognize them effectively, leading to detection failure (false-negative results). Efforts by EUTOS are focused on refining treatment strategies and establishing guidelines for managing these rare variants (13).

Guidelines from organizations, including the National Comprehensive Cancer Network, emphasize the necessity of detecting specific recurrent genetic abnormalities in bone marrow nucleated cells or peripheral blood leukocytes for optimal risk stratification and treatment planning (14). Recommended methodologies include cytogenetic analysis (karyotyping), interphase fluorescence *in situ* hybridization (FISH) and RT-PCR for fusion gene detection. Previous investigations have implemented RT-qPCR for *JAK2*, Calreticulin and myeloproliferative leukemia proto-oncogene gene analysis (15), supplemented with specialized primer sets targeting *BCR* exon (e)1, 12 and 3 to identify *BCR-ABL1* breakpoints, demonstrating comprehensive coverage of previously reported uncommon breakpoints (11,16). Bone marrow smear examination combined with FISH and karyotyping provides preliminary evidence of *BCR-ABL1* fusion (17). Next-generation sequencing (NGS) enables genomic analysis through fragmentation of genomic DNA or transcriptomic RNA, library preparation and high-throughput sequencing via fluorescence signal detection during polymerase/ligase-mediated nucleotide incorporation (18). For non-IS standardized transcripts, quantitative calibration and reporting methods, such as relative *ABL1* copy number analysis and laboratory-built reference curves, are recommended for improved quantification (19). Droplet digital (dd)PCR), with its defined detection limit and quantification limit, is a key tool for monitoring residual disease levels in these variants, with variant-specific primer design and stringent quality control procedures essential to ensure accuracy. Whole-genome sequencing (WGS) using exon capture techniques facilitates detection of *BCR-ABL1* fusions through comprehensive genomic interrogation (20). Additional methodologies, such as nested PCR coupled with agarose gel electrophoresis, have utility in detecting these transcripts, offering enhanced sensitivity and specificity compared with conventional techniques while enabling amplification of extended DNA fragments (21). Recent guidelines from European LeukemiaNet 2023 and EUTOS suggest regular monitoring of measurable residual disease using advanced techniques and more frequent follow-up for patients with atypical transcripts to improve patient management (6,22). Ongoing multicenter collaborations, such as the EUTOS study, are key in providing robust data on the clinical outcomes of these variants. These studies aim to validate the prognostic value of atypical BCR-ABL1 fusion genes and refine treatment strategies for these rare subtypes. Atypical *BCR-ABL1* testing should involve multiplex RT-PCR and NGS, followed by ddPCR for minimal residual disease monitoring, providing a structured approach to managing cases with atypical *BCR-ABL1* fusion genes (Fig. 1), with follow-up frequency and therapeutic adjustments based on patient response.

Current research on atypical fusion genes in leukemia remains exploratory, with knowledge gaps persisting. The low incidence of these genetic variants in leukemia populations has resulted in limited case reports (23,24), posing diagnostic and therapeutic challenges for clinicians managing patients with atypical fusion-positive CML. The present study aimed to review the structural characteristics therapeutic management, and prognostic implications of the *e13a3*, *e14a3, e1a3*, *e1a2*, *e6a2*, *e8a2*, *e19a2, e12a2* and *e13a1 BCR-ABL1* fusion transcripts to delineate their clinical significance (Figs. 2 and 3).

2. Materials and methods

The literature search was conducted using PubMed(pubmed.ncbi.nlm.nih.gov/), Embase (embase.com/landing?status=grey) and Web of Science(webofscience.com/wos/) from January 2000 to July 2025 using the following search strategy: ((BCR-ABL[Title/Abstract] OR BCR::ABL1[Title/Abstract]) AND (atypical[Title/Abstract] OR rare[Title/Abstract] OR e13a3 OR e14a3 OR e1a3 OR e1a2 OR e6a2 OR e8a2 OR e19a2 OR e12a2 OR e18a2 OR e13a1) AND (CML[Title/Abstract] OR 'chronic myeloid leukemia'[MeSH Terms] OR Ph + ALL[Title/Abstract]). A two-step 'include-then-exclude' process was performed: All case reports, series or retrospective studies in which atypical BCR-ABL1 transcripts were confirmed at the RNA or DNA level, the diagnosis met World Health Organization(WHO) criteria for CML or acute lymphoblastic leukemia(Ph^+ ALL) and both treatment details and evaluable follow-up outcomes were provided were eligible (25,26); conversely, reviews, editorials, animal studies lacking primary data and duplicate publications with overlapping cases were excluded, retaining only the most complete dataset for each patient. A total of two reviewers independently screened titles/abstracts, extracted

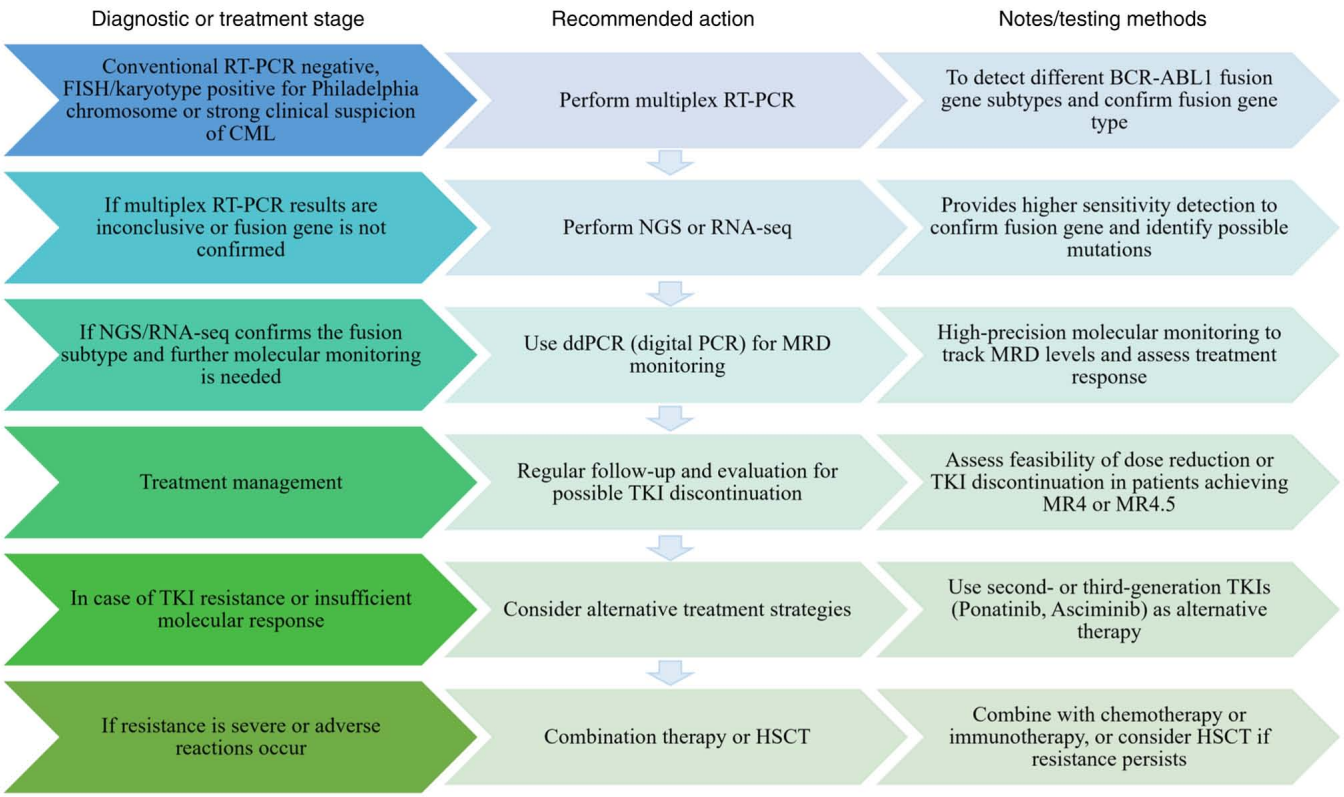

Figure 1. Clinical roadmap for atypical *BCR-ABL1* testing. BCR, breakpoint cluster region; ABL1, abelson leukemia1; RT-q, reverse transcription-quantitative; NGS, next-generation sequencing; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor; seq, sequencing; dd, digital droplet; MRD, minimal residual disease; MR, molecular response; HSCT, hematopoietic stem cell transplantation.

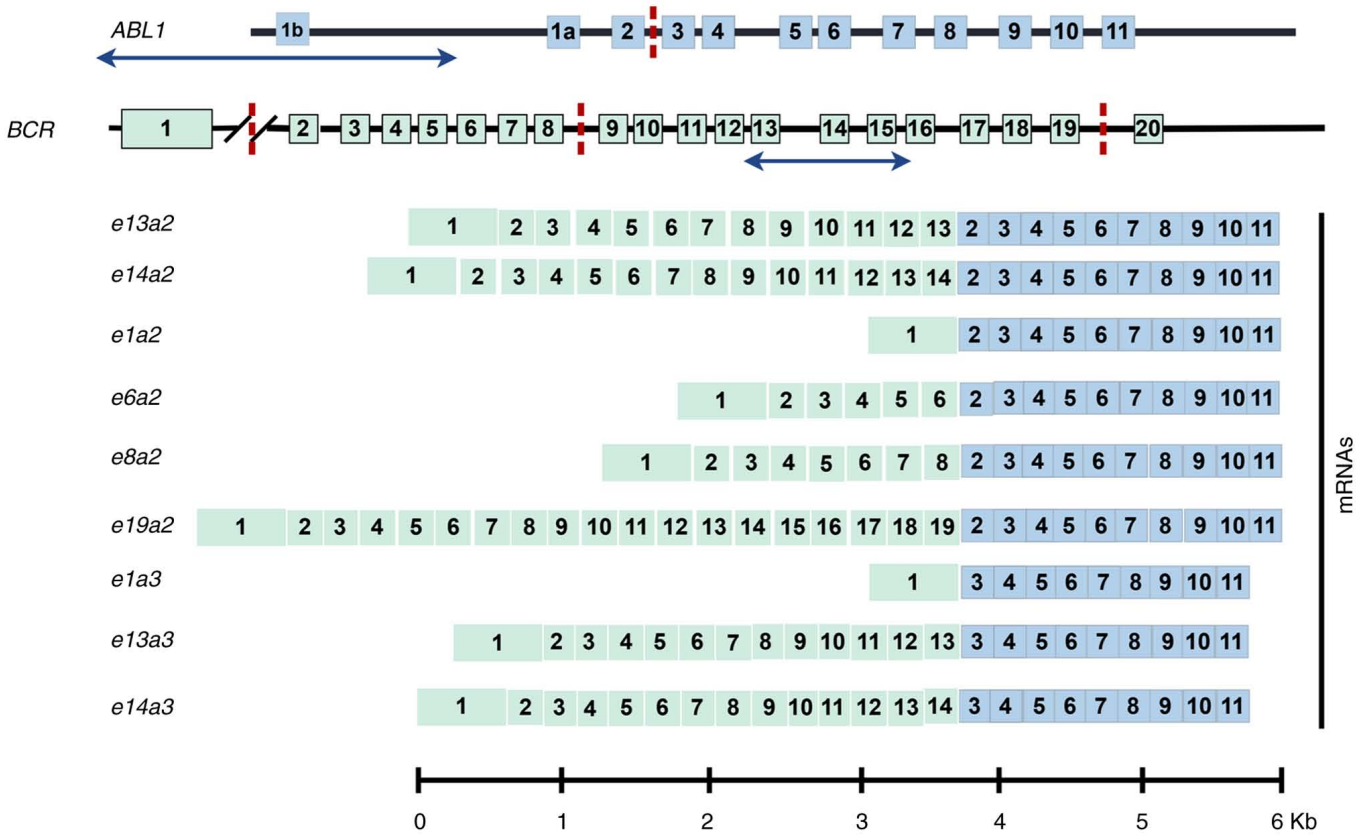

Figure 2. Schematic diagram of common and rare transcripts. Colors differentiate gene exons (with ABL1 in blue and BCR in red), arrows to indicate the direction of the gene, and dashed lines to represent mRNA splicing connections. Each mRNA splicing variant is composed of specific exon combinations, and a scale bar indicates the gene length. BCR, breakpoint cluster region; ABL1, abelson leukemia 1.

Table I. Evidence levels.

Subtype	Total cases (CML/Ph+ ALL)	Evidence type	Median follow-up, months (range)	Outcome definition	Evidence grade	(Refs.)
e13a3	38 (34/4)	Case series	24.0 (6.0-120.0)	CCyR, MMR, OS	B	(17,27,30,34,37,40,41,43,44)
e14a3	25 (22/3)	Case reports	18.0 (3.0-96.0)	CCyR, MMR	B	(11,21,53-57)
e1a3	12 (9/3)	Case reports	15.0 (3.0-60.0)	CNS relapse, OS	C	(60,64,69,72)
e1a2	41 (41/0)	Retrospective cohort	69.5 (12.0-120.0)	OS, blast crisis	A	(81,91,92,95-97)
e6a2	18 (15/3)	Case reports	12.0 (1.0-48.0)	ASCT outcomes	C	(63,65,66,100,102-104,140)
e8a2	5 (4/1)	Case reports	6.0 (3.0-36.0)	CHR, CMR	C	(107,109,110,116,141)
e19a2	22 (20/2)	Case series	30.0 (6.0-108.0)	MMR, TFR	B	(118,119,121,122,125, 129, 142-145)
e12a2	3 (3/0)	Case reports	72.0 (60.0-84.0)	MR4 sustained	C	(130,146)

Ph+ ALL data were separately analyzed and not extrapolated to CML outcomes. Only CML cases were used for prognostic estimations. CML, chronic myeloid leukemia; Ph, philadelphia chromosome; ALL, acute lymphoblastic leukemia; CCyR, complete cytogenetic response; MMR, major molecular response; OS, overall survival; CNS, central nervous system; ASCT, allogeneic stem cell transplantation; CHR, complete hematologic response; CMR, complete molecular response; TFR, treatment-free remission.

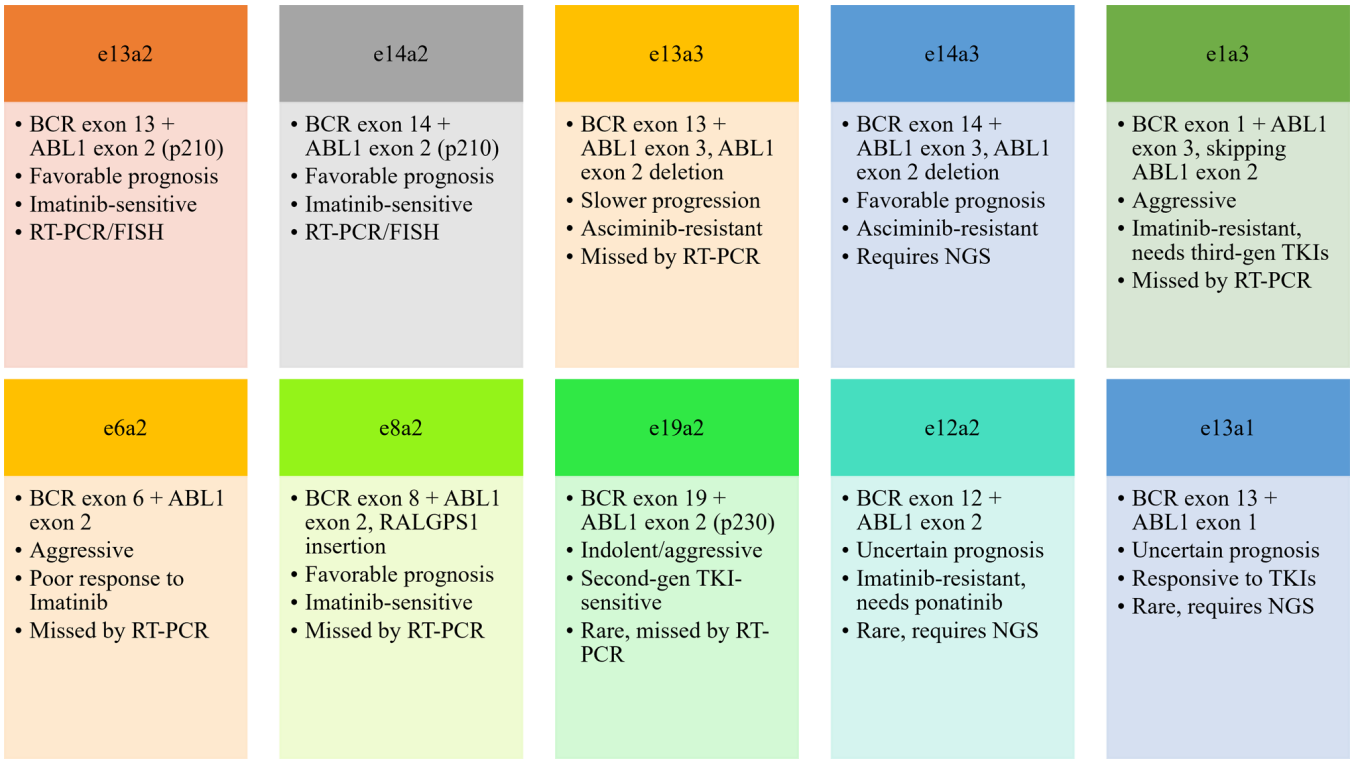

Figure 3. Atypical *BCR-ABL1* variants and their clinical significance. BCR-breakpoint cluster region; ABL1, abelson leukemia 1; RT, reverse transcription; FISH, fluorescence *in situ* hybridization; gen, generation; NGS, next-generation sequencing; TKI, tyrosine kinase inhibitor; RALGPS, Ral GEF with PH domain and SH3 binding motif.

data. Discrepancies resolved by a third reviewer. Because study designs varied widely, the present review conducted a descriptive synthesis. The PRISMA flowchart (Fig. 4) documents the systematic selection process. For each transcript subtype, the strength of evidence was graded hierarchically: Grade A (robust), ≥10 clinically annotated cases with a median follow-up ≥1 year; grade B (moderate), 3-9 cases or follow-up <1 year and grade C (limited), 1-2 cases or *in vitro* data only (Table I).

3. e13a3 variant

Structural characteristics. The *e13a3 (b2a3) BCR-ABL1* transcript is generated through direct linkage of e13 of the

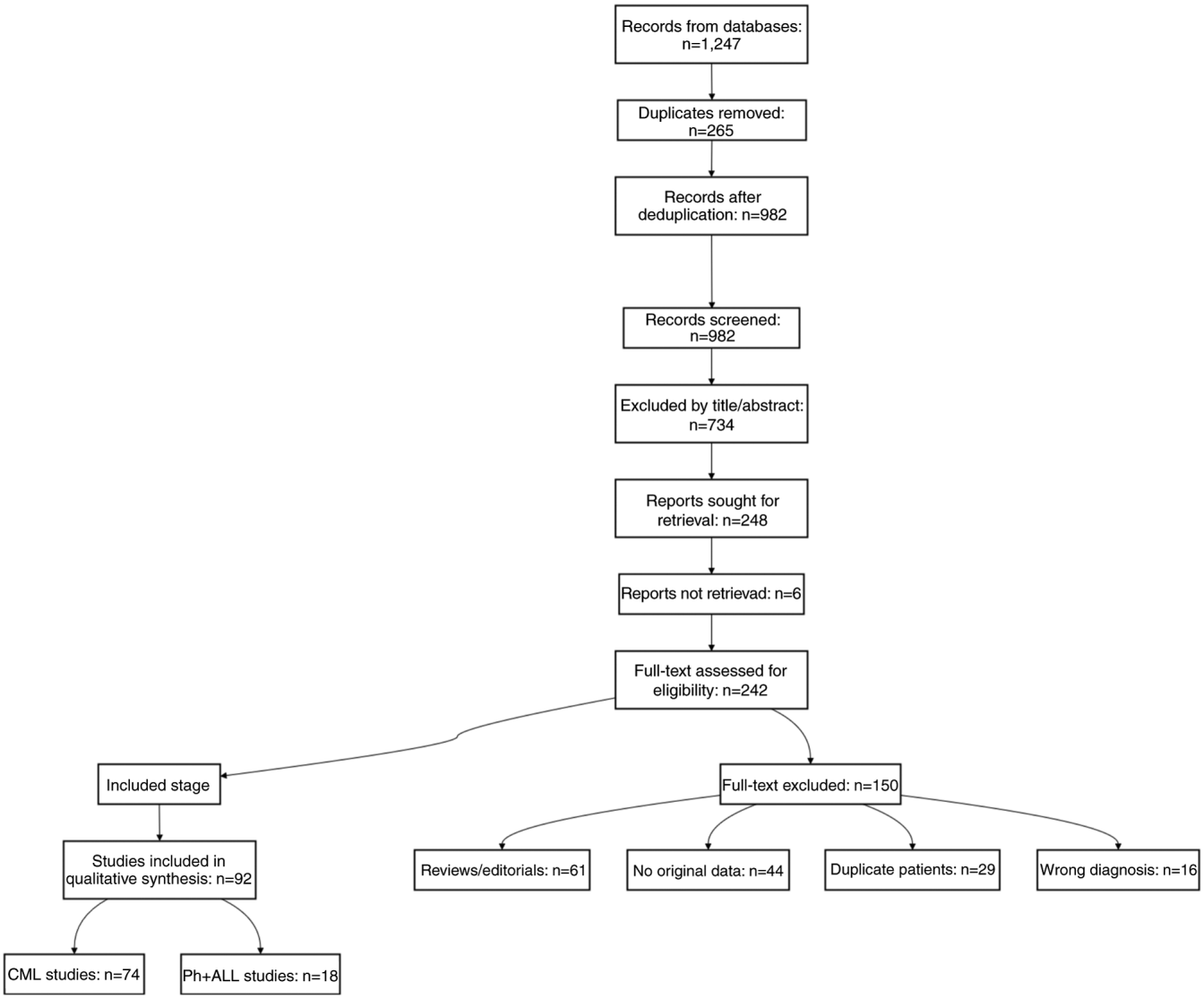

Figure 4. PRISMA flow diagram. CML, chronic myeloid leukemia; Ph, philadelphia chromosome; ALL, acute lymphoblastic leukemia.

BCR gene to e3 *(a3)* of the *ABL1* gene, resulting in deletion of *ABL1* e2 *(a2)*. This fusion produces a truncated protein that retains constitutively activated TK activity (27). The lack of the Src homology 3 (SH3) domain in this variant is linked to its unique structural properties, contributing to the formation of an SH3-deficient isoform. SH3 deficiency can impact downstream signaling, enhancing kinase activity and potentially promoting leukemogenesis (28). SH3-deficient variants such as *e13a3* are associated with altered protein interactions and subcellular localization, potentially affecting cell signaling pathways and contributing to disease progression. In murine models, *e13a3*, as an SH3-deficient variant, shows slower disease progression compared with canonical isoforms, though it retains leukemogenic potential, capable of inducing CML (29). This slower progression may be influenced by changes in cell adhesion, which alter the interaction between leukemic cells and the microenvironment, affecting disease dynamics. The SH3 domain normally serves as a negative regulator of ABL1 TK activity, and its deletion in the *e13a3* variant enhances kinase activity (7). The *e13a3* fusion breakpoint resides within the major breakpoint cluster region, resulting in the production of a 210 kDa (p210) fusion protein. Notably, the absence of the SH3 domain in the truncated *ABL1* moiety induces structural alterations in the chimeric protein. This aberrant protein retains constitutively activated TK activity, which drives leukemic cell proliferation and inhibits differentiation (27). Compared with canonical fusion subtypes such as *e14a2* or *e13a2*, this variant exhibits a unique genomic architecture (30). The *e13a3* transcript is predominantly observed in patients with chronic phase CML, with rare case reports in Ph chromosome-positive ALL (31-33). Notably, a Chinese study initially failed to detect the *e13a3* fusion using RT-qPCR, underscoring the risk of missing rare fusion subtypes when employing primer sets targeting conventional breakpoints, even in cases with confirmed *t(9;22)* translocation (17). Conversely, another study (34) documented a CML case with a normal karyotype and negative RT-PCR findings, where subsequent FISH analysis revealed *BCR-ABL1* fusion. This highlights the importance of multimodal diagnostic approaches, particularly when conventional methods yield equivocal results.

Therapeutic management. Imatinib, a first-generation TKI is widely utilized in *e13a3* variant CML. Most Ph-positive CML patients receiving 400 mg/day imatinib achieve complete cytogenetic remission (CCyR) within 6-12 months and maintain durable responses (35,36). McCarron *et al* (37) reported a 66-year-old male patient with Ph-positive CML who attained progressively deepening cytogenetic responses and declining *BCR-ABL1*/*ABL1* ratios following sustained 400 mg/day imatinib therapy. In Ph-negative CML cohorts (representing 5-10% of cases, characterized by *CR-ABL1* rearrangements undetectable by conventional cytogenetics) (38,39), studies (34,40) have evaluated second-generation TKIs including nilotinib. These agents demonstrate efficacy in achieving CCyR and major molecular response (MMR) in Ph-positive populations (17,27), which is consistent with the report by Zhou *et al* (41). Dasatinib, another second-generation TKI, has also been employed in this context. Mechanistic and *in vitro* studies indicate that the *e13a3* variant may exhibit resistance to asciminib, with clinical evidence remaining limited (7). Resistance observed in *e13a3* variant CML is largely based on laboratory-based research (7,42), and there is insufficient clinical data to support these findings.

Combination strategies integrating TKIs with chemotherapy have been explored. One notable example is the use of the ponatinib-fludarabine + Low-dose Cytarabine (Ara-C) + Granulocyte Colony-Stimulating Factor(G-CSF) + idarubicin regimen followed by allogeneic stem cell transplantation (ASCT), which resulted in molecular negativity and full donor chimerism at 19 months post-transplant in one case (43). Massimino *et al* (44) implemented a tailored approach in an 89-year-old male patient with mild renal impairment, including initial hydroxyurea (2,000 mg/day) for leukocytosis management, transitioning to dasatinib 100 mg/day, which achieved a deep molecular response (MR), characterized by a further reduction in transcript levels to undetectable. This strategy has also been used in other studies (17,30).

Prognostic outcomes. Most studies suggest that *e13a3*-positive patients exhibit a lower risk of progression to accelerated phase or blast crisis, with superior long-term event-free survival compared with rare variants such as *e1a2* or *e19a2* (12,45). Most patients attain deep, sustained responses following TKI monotherapy or combination regimens. A patient achieved complete hematological remission (CHR) at 2 months and MMR with RT-PCR negativity by 8 months, maintaining remission for 2 years (44). Another case demonstrated FISH-confirmed CCyR (0% *BCR-ABL1* fusion) at 6 months, sustained beyond 24 months (34). While certain TKI-treated cases exhibit persistent low-level e13a3 transcripts despite CCyR (37), combination therapies have shown favorable results. In addition to treatment efficacy, it is key to evaluate how the treatment regimen affects quality of life. Long-term use of TKIs can lead to side effects such as chronic fatigue, nausea and musculoskeletal pain, which may limit the ability to perform daily tasks and participate in social activities (46,47). Balancing treatment effectiveness with the impact on physical and emotional wellbeing is essential for optimal clinical decision-making. Resistance to treatment can develop due to ABL kinase mutations such as T315I or activation of compensatory signaling pathways such as PI3K/AKT and SRC, which allow the leukemic cells to survive despite the presence of TKIs (48). These mechanisms of resistance contribute to treatment failure and disease progression. In these cases, next-generation TKIs such as ponatinib and asciminib, which target resistant mutations, can be effective, although they may be associated with more severe side effects (49-51). Combining TKIs with other therapeutic modalities, including chemotherapy or stem cell transplantation, may be necessary for patients with resistant disease to achieve long-term disease control (52). Evidence on *e13a3* variant outcomes is summarized in Table II. Further multi-center studies are needed to validate these prognostic outcomes in CML.

4. e14a3 variant

Structural characteristics. In this fusion transcript, the *ABL1* breakpoint resides within intron 2, generating a chimeric mRNA linking *BCR* e14 to *ABL1* e3. This rearrangement induces structural and functional alterations in the fusion protein, dysregulating intracellular signaling pathways to promote leukemic cell proliferation, survival and immune evasion. A previous study employed customized RT-PCR coupled with Sanger sequencing to confirm this fusion mRNA (53), concurrently identifying non-synonymous mutations in *TP53*, FMS-like tyrosine kinase 3, KIT Proto-Oncogene, Receptor Tyrosine Kinase(*KIT)* and paired box 5, underscoring the molecular heterogeneity. Another case report documented methylenetetrahydrofolate reductase mutation in a patient with CML harboring this *BCR-ABL1* fusion, providing insights for future investigations (54). A study identified a *BCR-ABL1* fusion in a rare CML case, where the breakpoints occurred at *BCR* intron 14 and *ABL1* intron 2, using NGS (53). This unique fusion led to a compromised SH3 domain, which was associated with altered drug response and distinct clinical manifestations (53). These findings emphasize the critical role of SH3 domain loss in modulating therapeutic outcomes and the molecular heterogeneity underlying CML.

Therapeutic management. TKI monotherapy with imatinib or nilotinib has been used in *e14a3*-positive cases. A Chinese study (11) reported a 67-year-old Ph-positive female with coexisting *e13a3* and *e14a3* variants, the first documented instance of dual rare *BCR-ABL1* fusions in China, who achieved therapeutic response with imatinib. Vaniawala *et al* (55) reported *e14a3 BCR-ABL1* fusion in a 30-year-old male managed solely with imatinib. Nilotinib was similarly employed to treat a 52-year-old male by Massimino *et al* (56), with both cases achieving a treatment response.

Personalized combination regimens have also been explored. In a study by Lyu *et al* (53), hydroxyurea was initially administered for rapid leukocytosis control prior to TKI initiation, with subsequent imatinib dose reduction (from 400 to 300 mg/day) due to intolerance, emphasizing individualized dosing. A previous study (57) reported sequential intolerance to imatinib and dasatinib, ultimately transitioning to hydroxyurea monotherapy.

Prognostic outcomes. Most patients with *e14a3* variant CML exhibit favorable prognoses, achieving sustained hematological, cytogenetic and molecular remissions. In a

Chinese cohort (11), imatinib monotherapy induced rapid MR, with CCyR attainment within 3 months and notable *BCR-ABL1-e14a3* transcript reduction. Nilotinib-treated cases similarly demonstrated favorable outcomes (56). Combination regimens have shown variable efficacy: One study reported TKI monotherapy achieving CHR at 2 months, MMR at 3 months and sustained transcript negativity for 9 years without kinase domain mutations (21). Adjuvant agents such as interferon, hydroxyurea, and aspirin were incorporated, though immunomodulatory effects of interferon yielded inconsistent results compared with prior reports (57,58). Conversely, a patient requiring hydroxyurea-nilotinib combination therapy achieved hematological and molecular remission after dose adjustment (54). Key *e14a3* variant case reports and outcomes are summarized in Table III.

5. e1a3 variant

Structural characteristics. The *e1a3* transcript arises from direct fusion of *e1* of the *BCR* gene to *e3 (a3)* of the *ABL1* gene, skipping *ABL1 e2 (a2)*. This structural alteration results in a truncated fusion protein lacking approximately two-thirds of the sequence encoding the SH3 domain within the *ABL1* moiety (8). Distinct from common variants, its unique fusion junction may perturb subcellular localization, substrate specificity and signaling pathways, thereby disrupting cellular homeostasis. This transcript is relatively rare, with a single case (4.8%) identified among patients with CML in a Syrian study (59). Additionally, its occurrence has been documented in Ph^+ ALL and AML (31). Some researchers have posited that a subset of *e1a3 BCR-ABL1*-positive ALL cases may represent undiagnosed CML in lymphoid blast crisis, requiring exclusion through comprehensive clinical history review (60). A previous study (61) identified multiple atypical *BCR-ABL1* transcripts in CML, challenging prior assumptions of singular fusion dominance. Conventional RT-PCR frequently fails to detect these transcripts, often yielding false-negative results (62), while RNA sequencing (RNA-seq) uncovers their presence, highlighting the necessity for advanced molecular diagnostics in clinical practice. The *e1a3* and *e6a2 BCR-ABL1* transcripts are characterized by unique fusion breakpoints within the *ABL1* gene (63,64). These isoforms are less common and associated with more aggressive disease progression, including early blast crisis and resistance to standard TKIs (65,66). These isoforms demonstrate TKI resistance and often require multimodal therapy, including the use of third-generation TKIs or stem cell transplantation (67,68).

Therapeutic strategies. Unlike e13a3 and e14a3 variants, dasatinib serves as the primary TKI for e1a3-positive CML. The majority of reported cases demonstrate an indolent clinical course (62,69). A previous study (64) reported a patient achieving CCyR following immediate dasatinib initiation (140 mg/day). An 80-year-old Ph-positive male treated with 400 mg/day imatinib attained rapid CCyR and hematological normalization but subsequently developed lymphoblastic crisis at 5 months, suggesting a risk of ALL transformation (8). Combination therapies, including dasatinib with nilotinib or ponatinib, have shown variable efficacy (68,70); the T315I mutation frequently serves as the primary resistance mechanism, necessitating the switch to third-generation TKIs (71).

Innovative approaches, such as third-generation TKIs combined with ASCT, have been employed in a previous study (72). A 56-year-old female patient maintained disease-free status post-ASCT with continued olverembatinib therapy, underscoring the potential of next-generation TKIs and ASCT in managing this rare subtype (72).

Prognostic outcomes. Prognoses for *e1a3* variant CML patients exhibit marked heterogeneity. A Japanese male (64) achieved CCyR by 6 months with dasatinib, despite presenting with extramedullary leukemia lacking leukocytosis, which is rare in CML. A previous case (72) demonstrated sustained remission post-ASCT and olverembatinib maintenance, yet developed isolated central nervous system (CNS) infiltration without hematological/cytogenetic relapse, implicating the CNS as a potential sanctuary site. Due to the blood-brain barrier and relatively immune-privileged status, conventional systemically administered chemotherapeutic and targeted therapeutic agents often fail to achieve effective concentrations within the CNS. This allows cancer cells to evade treatment, survive, and cause a relapse in this sanctuary site, while the rest of the body may still be in a state of remission. A patient harboring the *e1a3* fusion, typically associated with aggressive disease, maintained stable, untreated CML, challenging the association between *BCR-ABL1* variants and clinical severity (64). Key *e1a3* variant case reports and outcomes are summarized in Table IV.

6. e1a2 variant

Structural characteristics. The *e1a2* variant arises from fusion between e1 of the *BCR* gene and e2 of the *ABL1* gene, generating a chimeric protein with distinct structural and functional properties. By contrast with the canonical p210 isoform, the p190 variant lacks central e13 and 14 of the *BCR* gene. Despite this truncation, the p190 fusion protein retains notably enhanced TK activity, which remains sufficient to drive leukemogenesis (73,74). The *e1a2* transcript is rare in CML, accounting for ~1.8% of cases in a cohort of 2,322 patients treated with TKIs, including 1,326 male and 996 female patients, with a median age of 48 years (range 18-88) (14,75), In the aforementioned study, 41 patients (1.8%) exhibited the *e1a2* fusion, confirmed by RT-PCR. This variant is associated with a distinct phenotype marked by monocytosis, absence of basophilia and blast crisis presentation at initial diagnosis in 61% of cases, significantly higher than in patients with canonical transcripts (76). In a study by Gong *et al* (52), 16 of 41 patients with the *e1a2* transcript presented with blast crisis at initial diagnosis, two had accelerated phase and 23 were in chronic phase (76) The frequency of monocytosis at initial diagnosis was confirmed in 10 patients with available blood counts, showing a median of 11.5% (range, 5-36%), with seven patients exhibiting monocytosis >10% (76). In Ph-positive adult ALL, the *e1a2* variant accounts for 61.2% of cases, as reported in a national cohort of 67 patients with Ph^+ ALL, and is typically associated with elevated leukocyte count and lymphoid lineage differentiation (77). RT-PCR for *BCR-ABL1* detection, and

Table II. Summary of existing reports on cases associated with the *e13a3* variant.

Type	Country	Age, years	Sex	Method	Treatment	Outcome	Follow-up duration	Diagnosis stage	Mutations	Adjustment	Transplantation	Adverse reactions	Cause of death	(Refs.)
CML Ph(-)	Japan	37	F	FISH, RT-PCR	TKI: Imatinib, 400 mg/day	CHR, MMR	12 months	Chronic phase	None	No adjustment	No transplantation	Fatigue	None	(40)
CML Ph(-)	China	24	F	FISH, RT-PCR, gene sequencing	TKI: Imatinib 400 mg/day	CCyR	18 months	Chronic phase	None	No adjustment	No transplantation	Nausea	None	(34)
CML Ph(+)	China	39	M	RT-PCR, Sanger sequencing	TKI: Nilotinib, 300 mg/day	MMR	12 months	Chronic phase	None	No adjustment	No transplantation	Fatigue	None	(41)
CML Ph(+)	UK	30	M	RT-PCR	TKI: Ponatinib, 45 mg/day. Non-TKI: FLAG-IDA, allo-ASCT	MMR	24 months	Chronic phase	None	No adjustment	Allo-ASCT	Gastrointestinal disturbances	None	(43)
CML Ph(+)	Japan	49	M	RT-PCR, FISH	TKI: Imatinib, 400 mg/day. Non-TKI: Interferon, hydroxyurea	MMR	12 months	Chronic phase	None	No adjustment	No transplantation	Nausea	None	(30)
CML Ph(+)	Korea	57	M	RT-PCR, Sanger sequencing, multiplex RT-PCR	TKI: Nilotinib, 300 mg/day. Non-TKI: Interferon, Hydroxyurea	CCyR, MMR	18 months	Chronic phase	None	No adjustment	No transplantation	Fatigue	None	(27)
CML Ph(+)	China	32	M	RT-qPCR, FISH, karyotype analysis	TKI: 300 mg/day nilotinib. Non-TKI: Hydroxyurea	CCyR	18 months	Chronic phase	None	No adjustment	No transplantation	Gastrointestinal disturbances	None	(17)
CML Ph(+)	Italy	89	M	G-banding, multiplex RT-PCR, Sanger sequencing	TKI: Dasatinib, 50 mg/day. Non-TKI: Hydroxyurea	CCyR, but e13a3 BCR-ABL1 transcript remains	24 months	Chronic phase	None	No adjustment	No transplantation	Nausea	None	(44)
CML Ph(+)	Ireland	66	M	Genetic analysis, qPCR	TKI: Imatinib, 400 mg/day	BCR-ABL1 transcripts are decreased	12 months	Chronic phase	None	No adjustment	No transplantation	Nausea	None	(37)

FISH, fluorescence *in situ* hybridization; RT, reverse transcription; qPCR, quantitative; TKI, tyrosine kinase inhibitor; CCyR, complete cytogenetic response; MMR, major molecular response; M, male; F, female; CML, chronic myeloid leukemia; Ph, philadelphia chromosome.

Table III. Summary of existing reports on cases associated with the *e14a3* variant.

Type	Country	Age, years	Sex	Method	Treatment	Outcome	Follow-up duration	Diagnosis stage	Mutations	Adjustment	Transplantation	Adverse reactions	Cause of death	(Refs.)
CML Ph(+)	China	24	M	RT-PCR, Sanger sequencing, NGS	TKI: Imatinib, 400 mg/day. Non-TKI: Hydroxyurea	Imatinib is tolerated after lowering the dosage	18 months	Chronic phase	None	Dose was decreased to 300 mg/day	No transplantation	Fatigue	None	(53)
CML Ph(+)	USA	81	M	FISH, Cytogenetic analysis, RT-qPCR, DNA Sequencing	TKI: Dasatinib, 50 mg/day; imatinib, 400 mg/day. Non-TKI: Hydroxyurea	PCyR	12 months	Chronic phase	None	No adjustment	No transplantation	Fatigue, gastrointestinal disturbances	None	(57)
CML Ph(+)	USA	54	F	RT-qPCR, FISH	TKI: Nilotinib, 300 mg/day Non-TKI: Hydroxyurea	CHR, MMR	18 months	Chronic phase	None	No adjustment	No transplantation	Nausea, fatigue	None	(54)
CML Ph(+)	China	67	F	RT-qPCR	TKI: Imatinib, 400 mg/day	CCyR	24 months	Chronic phase	None	No adjustment	No transplantation	Fatigue	None	(11)
CML Ph(+)	China	41	F	FISH, nested PCR, qPCR	TKI: Imatinib, 400 mg/day; dasatinib, 50 mg/day; nilotinib, 300 mg/day. Non-TKI: Hydroxyurea, interferon	MMR	24 months	Chronic phase	None	No adjustment	No transplantation	Gastrointestinal disturbances	None	(21)
CML Ph(+)	Italy	52	M	Cytogenetic analysis, multiplex, RT-PCR	TKI: Imatinib, 400 mg/day; dasatinib, 50 mg/day; nilotinib 300 mg/day	CHR, CCyR	18 months	Chronic phase	None	No adjustment	No transplantation	Nausea, fatigue	None	(56)
CML Ph(+)	India	30	M	Cytogenetic analysis, FISH, RT-PCR	TKI: Imatinib, 400 mg/day. Non-TKI: Allo-ASCT	CHR	24 months	Chronic phase	None	No adjustment	Allo-ASCT	None	None	(55)

FISH, fluorescence *in situ* hybridization; RT, reverse transcription; q, quantitative; TKI, tyrosine kinase inhibitor; PCyR, partial cytogenetic response; CHR, complete hematologic response; NGS, next-generation Sequencing; MMR, major molecular response; Allo-ASCT, allogeneic stem cell transplantation; M, male; F, female; CML, chronic myeloid leukemia; Ph, philadelphia chromosome.

Table IV. Cases associated with the *e1a3* variant.

Type	Country	Age, years	Gender	Method	Treatment	Outcome	Follow-up duration	Diagnosis stage	Mutations	Adjustment	Transplantation	Adverse reactions	Cause of death	(Refs.)
CML Ph(+)	Japan	49	M	FISH, RT-PCR, Sanger Sequencing	TKI: Dasatinib, 50 mg/day	CCyR	12 months	Chronic phase	None	No adjustment	No transplantation	Fatigue, mild nausea	None	(64)
CML Ph(+)	Spain	80	M	FISH, RT-PCR, Cytomolecular assays	TKI: Imatinib, 400 mg/day	Lymphoblastic crisis	6 months	Blast crisis	None	No adjustment	No transplantation	Severe fatigue, gastrointestinal disturbances	Lymphoblastic transformation	(60)
CML Ph(+)	Spain	75	F	RT-PCR	TKI: Imatinib, 400 mg/day	In good condition	24 months	Chronic phase	None	No TKI	No treatment	No transplantation	None	(69)
CML Ph(+)	China	56	F	FISH, RT-PCR, FC	TKI: Flumatinib, 50 mg/day; orebatinib, 50 mg/day. Non-TKI: Chemotherapy, allo-ASCT	Disease-free	24 months	Chronic phase	None	No adjustment	Yes, Allo-ASCT	None	None	(71)

FISH, fluorescence *in situ* hybridization; RT, reverse transcription; q, quantitative; TKI, tyrosine kinase inhibitor; CCyR, complete cytogenetic response; PCyR, partial cytogenetic response; CHR, complete hematological response; NGS, next-generation sequencing; MMR, major molecular response; Allo-ASCT, allogeneic hematopoietic stem cell transplantation; FC, flow cytometry; M, male; F, female; CML, chronic myeloid leukemia; Ph, philadelphia chromosome.

Sanger sequencing are employed to confirm atypical fusion transcripts.

Therapeutic strategies. Imatinib remains the primary therapeutic agent for *e1a2*-positive leukemia. A standard initial dose of 400 mg/day is administered in patients with ALL and CML, with dose escalation or TKI switching considered for suboptimal responders. However, it is important to consider the impact of side effects on daily life (78). Common adverse reactions such as fatigue, gastrointestinal disturbance and skin rashes can significantly disrupt daily activities and affect the overall quality of life (79). These side effects should be weighed when selecting the most appropriate treatment regimen, and supportive care may be necessary to improve patient comfort during therapy (80). A previous study (81) documented a patient with Ph-negative CML achieving molecular remission (undetectable *e1a2 BCR-ABL1* by RT-PCR) after 2 months of imatinib monotherapy, alongside rare cyclical leukocyte fluctuations and spontaneous normalization without intervention. However, resistance to TKIs is a major challenge, particularly in patients with mutations in the ABL kinase domain, such as the T315I mutation, which notably impairs the binding of TKIs to the *BCR-ABL1* fusion protein (82,83). These mutations lead to decreased efficacy of first- and second-generation TKIs. Additionally, compensatory signaling pathways, including the PI3K/AKT and SRC kinase pathways, may be activated, allowing leukemic cells to bypass the inhibition of *BCR-ABL1*, contributing to treatment resistance (84). To overcome these mechanisms of resistance, third-generation TKIs such as ponatinib and asciminib, which are designed to target *BCR-ABL1* with T315I mutations and other resistant forms, show promising results (50,51,85). However, these agents also cause more severe side effects, including cardiovascular complications, which should be managed. Combining TKIs with other therapeutic strategies, such as chemotherapy or immunotherapy, may provide an alternative approach to overcome resistance, but this requires consideration of the risk-to-benefit ratio for each patient (86-89).

Combination approaches are frequently employed, often incorporating consolidation chemotherapy post-remission (68,90). Japanese protocols (91) combine hydroxyurea with TKIs. For relapsed/refractory cases, TKI substitution or chemotherapy intensification may be pursued. A previous study (92) reported initial imatinib-induced symptom resolution and 2.5-log *BCR-ABL1* reduction, followed by leukemic transformation at 6 months necessitating high-dose chemotherapy and nilotinib. Transcript isoform switching may be a potential molecular mechanism underlying disease recurrence (93).

Prognostic outcomes. Prognostic heterogeneity characterizes *e1a2* variant CML. While some patients achieve durable remission with imatinib-based regimens (81,92,94,95), clonal dynamics complicate outcomes. Multivariable analyses have confirmed that *e1a2 BCR-ABL1* serves as an independent adverse prognostic factor, with a median OS of 69.5 months. Given its clinical behavior resembling Ph-positive ALL, certain researchers advocate classifying *e1a2* as a distinct high-risk subtype of CML (76). One case (96) harbored dual *e13a3* and *e1a2* clones, developing imatinib resistance linked to *e1a2* persistence despite achieving CHR, ultimately progressing to blast crisis and death. Notably, resistance occurred without *ABL1* kinase domain mutations, suggesting alternative mechanisms. A separate study (97) described extramedullary blast crisis at TKI initiation, mirroring *e1a3* cases, yet subsequent multimodal therapy (TKIs, ASCT) achieved sustained complete molecular remission (CMR) for >48 months. These findings underscore the necessity for comprehensive molecular monitoring and adaptive therapeutic strategies. Key *e1a2* variant case reports and outcomes are summarized in Table V.

7. e6a2 variant

Structural characteristics. *e6a2* variant results from fusion between e6 of the *BCR* gene and e2 of the *ABL1* gene. This rearrangement alters the fusion protein structure, conferring distinct TK activity and protein interaction profiles compared with common variants, thereby dysregulating multiple intracellular signaling pathways to drive leukemogenesis (98). This transcript accounts for 0.02-2.30% of all *BCR-ABL1*-positive CML cases. Although most patients present in chronic phase, up to 40% of cases are diagnosed in accelerated phase or blast crisis, with this variant frequently demonstrating an aggressive clinical course (9,65). This transcript was also detected in a case of ABL (99). Notably, conventional RT-qPCR may fail to detect the *e6a2 BCR-ABL1* transcript, necessitating specialized RT-PCR strategies for rare fusion detection (66). Zagaria *et al* (100) employed ddPCR for *e6a2* transcript quantification, leveraging its high sensitivity, absolute quantification without standard curves and multiplexing capabilities. Concurrent additional sex combs-like 1(*ASXL1)* mutations, identified via NGS in *e6a2*-positive cases, may synergize with the fusion to promote acute transformation (65). Domains retained or missing in each subtype fusion protein are presented in Table VI.

Therapeutic strategies. TKIs including imatinib (101), nilotinib (63) and dasatinib (102) are used for *e6a2* variant management, with imatinib remaining the cornerstone. However, certain scholars advocate upfront use of second-generation TKIs or ASCT to circumvent suboptimal responses to imatinib (103). In one CML case (102), initial hydroxyurea therapy for thrombocytosis was discontinued due to neutropenia, followed by successful imatinib 400 mg/day administration. *In vitro* sensitivity assay measuring Crk-like protein and phosphorylated-Src family kinase (Tyr416) inhibition confirmed imatinib responsiveness, guiding therapeutic decisions (103).

Combination regimens integrating chemotherapy and TKIs are employed in refractory cases. Crampe *et al* (65) reported a patient achieving hematological and morphological remission (*BCR-ABL1/ABL1*: 0.06%) with imatinib dose escalation (from 400 to 600 mg/day), though subsequent sepsis necessitated allogeneic ASCT. Furthermore, targeted therapies may confer prognostic benefits in patients harboring co-occurring *ASXL1* mutations.

Prognostic outcomes. Prognoses for *e6a2* variant CML exhibit marked variability, with frequent fatal outcomes. While some

Table V. Cases associated with the *e1a2* variant.

Type	Country	Age	Gender	Method	Treatment	Outcome	Follow-up duration	Diagnosis stage	Mutations	Adjustment	Transplantation	Adverse reactions	Cause of death	(Refs.)
CML Ph(+)	USA	23	F	G-banding, FISH, PCR	TKI: Imatinib, 400 mg/day; dasatinib, 50 mg/day. Non-TKI: Chemotherapy, ASCT	MMR	12 months	Blast crisis	None	No adjustment	Yes, Allo-ASCT	Fatigue, nausea	None	(97)
CML Ph(-)	Serbia	32	M	FISH, RT-PCR, Southern blotting	TKI: Imatinib, 400 mg/day	CHR, MMR	18 months	Blast crisis	None	No adjustment	No transplantation	Mild nausea, fatigue	None	(81)
CML Ph(+)	Japan	77	M	RT-PCR	Non-TKI: Hydroxyurea	Death	6 months	Blast crisis	None	No treatment	No transplantation	Severe fatigue, GI disturbances	DIC and respiratory failure	(91)
CML Ph(+)	UK	53	M	Sanger sequencing, cytogenetic analysis	TKI: Imatinib, 400 mg/day; nilotinib, 300 mg/day Non-TKI: FLAG-Ida, ASCT	MMR	18 months	Blast crisis	None	No adjustment	Allo-ASCT	Mild fatigue	None	(92)
CML Ph(+)	Ireland	61	F	RT-PCR,	TKI: Imatinib, 400 mg/day. Non-TKI: Hydroxyurea	CHR, CCyR	24 months	Blast crisis	None	No adjustment	No transplantation	Mild fatigue	None	(95)
CML Ph(+)	Spain	79	F	Cytogenetic analysis, FISH, RT-PCR, Southern blotting	TKI: Imatinib 400 mg/day	Death	12 months	Blast crisis	None	No adjustment	No transplantation	Severe fatigue, GI disturbances	Death	(96)

FISH, fluorescence *in situ* hybridization; RT, reverse transcription; q, quantitative; TKI, tyrosine kinase inhibitor; CCyR, complete cytogenetic response; PCyR, partial cytogenetic response; CHR, complete hematological response; NGS, next-generation sequencing; MMR, major molecular response; Allo-ASCT, allogeneic stem cell transplantation; M, male; F, female; CML, chronic myeloid leukemia; Ph, philadelphia chromosome; DIC, disseminated intravascular coagulation.

Table VI. Comparison of *BCR-ABL1* fusion protein domains.

Fusion protein	Retained domains	Missing domains	Biological implications
e6a2	BCR coiled-coil, DBL/PH, TK	SH3	Loss of SH3 domain may contribute to dysregulated signaling, associated with resistance to TKI therapy
e13a3	BCR coiled-coil, DBL/PH, TK	SH3	Loss of SH3 enhances kinase activity, promoting unregulated cell proliferation and leukemia development
e14a3	BCR coiled-coil, DBL/PH, TK	SH3	Alterations in SH3 may affect cellular signaling, potentially influencing TKI response
e1a3	BCR coiled-coil, TK	DBL/PH, SH3	Missing SH3 and DBL/PH domains disrupt signaling pathways, leading to aggressive disease progression.

DBL/PH, diffuse B cell lymphoma/pleckstrin homology; TK, tyrosine kinase; SH3, src homology 3; BCR, breakpoint cluster region.

achieve sustained remission post-TKI monotherapy (63,102) or ASCT (65), others experience rapid progression. Prognostic indices indicate that despite a subset of patients exhibiting low-risk Sokal scores (63), OS rates remain inferior to those observed in patients with common transcript subtypes. A patient with Ph-positive CML maintained CCyR for 6 months on dasatinib despite notable eosinophilic hyperplasia with atypical precursors (a morphology potentially linked to the *e6a2* transcript) (100). Conversely, Beel *et al* (66) documented rapid blast crisis within 3 months of TKI initiation, culminating in fatal multidrug-resistant bacteremia post-ASCT. Rohon *et al* (103) advocated early ASCT or clinical trial enrollment for *e6a2*-positive cases following short-term TKI or dual *Src/ABL* inhibitor therapy.

Aggressive presentations include iliac sarcoma at diagnosis (104) and novel *BCR-ABL1* kinase domain mutations (*K245E, L284S*) emerging during imatinib therapy, culminating in blast crisis CML and death (105). These findings underscore the need for personalized strategies addressing variant-specific biology. Key *e6a2* variant case reports and outcomes are summarized in Table VII.

8. e8a2 variant

Structural characteristics. The *e8a2* variant is rare in CML cases. It is characterized by fusion between e8 of the *BCR* gene and exon a2 of *ABL1*, with insertion of a 127-bp sequence from e8 of Ral GEF with PH domain and SH3 binding motif 1 (106). Studies demonstrate that the generation of this transcript requires at least three chromosomal breaks (106,107): The first occurs within *ABL1 intron 1b,* causing inversion and insertion of this region downstream of *BCR* e8; the second occurs at *BCR* intron 8, facilitating fusion of *BCR* e8 with *ABL1 a2*; the third may involve additional chromosomes, forming a four-way translocation (107). While the *BCR-ABL1 e8a2* transcript is predominantly observed in CML, its occurrence in ALL remains rare (106,108). A Uruguayan study (109) documented a rare four-way translocation *t(1;17;9;22)(p35;q24;q44;q11)* in a 51-year-old female patient with *e8a2*-positive CML, highlighting the complexity of chromosomal rearrangements in leukemogenesis. Researchers (110) have identified somatic mutations in tumor protein p53 binding protein 2 and cadherin-10 via whole-exome sequencing, absent in typical CML or healthy controls, suggesting potential *BCR-ABL1*-driven mutagenesis. Burmeister *et al* (107) proposed a mechanistic model for cryptic exon activation, generating transcripts containing 55-bp *ABL1* intron 1b sequences. While the 55-bp insertion has been suggested as a potential prerequisite for sustaining kinase activity (111), documented cases demonstrate that insertion-free *e8a2* retains oncoprotein-coding capacity, suggesting molecular heterogeneity (112,113). The *e8a2* and *e19a2* variants are rare and associated with complex chromosomal rearrangements. These variants can be considered distinct from typical *BCR-ABL* transcripts. due to their distinct structural features, including the involvement of additional chromosomal breaks that contribute to unique functional properties of the fusion proteins. These isoforms are less commonly associated with early TKI resistance but are often found in patients with advanced disease or when conventional diagnostic techniques fail.

Therapeutic strategies. TKI regimens (imatinib, dasatinib, nilotinib) constitute the primary therapeutic approach for *e8a2*-positive CML, often supplemented by individualized protocols. Dasatinib is prioritized as frontline therapy (110), with adjunctive measures such as thromboprophylaxis and allopurinol administration tailored to patient-specific factors, including age, comorbidity and disease phase. Close clinical monitoring ensures timely regimen optimization.

Prognostic outcomes. Most patients with e8a2 variant CML show a tendency towards favorable outcomes under TKI therapy (114); while initial studies associated the e8a2 transcript with thrombocytosis and suggested a poorer prognosis, more recent findings indicate that prognosis may vary, and the evidence remains inconclusive (107,115). Imatinib-treated cases typically demonstrate robust responses, while interferon-intolerant patients achieve CHR and CMR (BCR-ABL1 <0.001%) within 6 weeks, sustained beyond 6 months (110).

Table VII. Cases associated with the *e6a2* variant.

Type	Country	Age, years	Gender	Method	Treatment	Outcome	Follow-up duration	Diagnosis stage	Mutations	Adjustment	Transplantation	Adverse reactions	Cause of death	(Refs.)
CML Ph(+)	Italy	49	M	Cytogenetic testing, FISH, RT-PCR, ddPCR	TKI: Dasatinib, 100 mg/day	CCR	12 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(100)
CML Ph(+)	Ireland	48	F	Sanger sequencing, RT-qPCR, NGS	TKI: Imatinib, 400 mg/day. Non-TKI: Induction therapy, allo-ASCT	CHR, MMR	18 months	Chronic phase	None	Dose reduction	Allo-ASCT	Mild nausea, fatigue	None	(65)
CML Ph(+)	Belgium	57	M	TaqMan RQ-PCR, FISH, RT-qPCR	TKI: Imatinib, 400 mg/day. Non-TKI: Leukapheresis and chemotherapy, Allo-ASCT	Death	6 months	Accelerated phase	None	No adjustment	Allo-ASCT	Severe nausea, GI distress	Sepsis	(66)
CML Ph(+)	Czech Republic	51	M	RT-PCR, sequencing	TKI: Imatinib, 400 mg/day. Non-TKI: Hydroxyurea, G-CSF, allo-ASCT	MMR	24 months	Chronic phase	None	No adjustment	Allo-ASCT	Mild fatigue	None	(103)
CML Ph(+)	Italy	43	M	FISH, RT-PCR	TKI: Imatinib, 400 mg/day. Non-TKI: Hydroxyurea	CCyR	18 months	Chronic phase	None	No adjustment	No transplantation	Mild nausea	None	(102)
CML Ph(+)	Italy	46	F	RT-PCR, Sanger sequencing	TKI: Nilotinib 300 mg/day	CHR, CCyR	12 months	Chronic phase	None	No adjustment	No transplantation	Mild nausea, fatigue	None	(63)
CML Ph(+)	Portugal	18	F	RT-PCR	TKI: Imatinib, 400 mg/day. Non-TKI: Radiotherapy, chemotherapy	Death	3 months	Acute lymphoblastic leukemia	None	No adjustment	No transplantation	Severe nausea, fatigue	Leukemic transformation	(104)
CML Ph(+)	Germany	48	M	FISH, multiple RT-PCR	TKI: Imatinib, 400 mg/day; dasatinib 50 mg/day	Death	8 months	Chronic phase	None	No adjustment	No transplantation	Severe fatigue, GI distress	Sepsis	(140)

M, male; F, female; CML, chronic myeloid leukemia; Ph, philadelphia chromosome; FISH, fluorescence *in situ* hybridization; RT, reverse transcription; q, quantitative; TKI, tyrosine kinase inhibitor; CCyR, complete cytogenetic response; PCyR, partial cytogenetic response; CHR, complete hematological response; NGS, next-generation sequencing; MMR, major molecular response; Allo-ASCT, allogeneic hematopoietic stem cell transplantation; dd, digital droplet; G-CSF, granulocyte colony-stimulating factor.

Tchirkov *et al* (116) validated real-time RT-PCR for precise molecular monitoring, enabling therapeutic efficacy assessment and relapse prediction. Key e8a2 variant case reports and outcomes are summarized in Table VIII.

9. e19a2 variant

Structural characteristics. The e19a2 (μ-BCR-ABL1) transcript arises from aberrant fusion of BCR intron 19 to ABL1 exon a2, encoding a 230-kDa fusion protein (117). Its formation involves submicroscopic insertion events, resulting in FISH-negative/RT-PCR-positive detection. While p230 retains BCR oligomerization domains and ABL1 TK activity, structural divergence from p210 may compromise kinase-dependent signaling efficiency. Sequencing of cDNA microproducts (118) has identified mutations in ABL1 e4-9, while WGS uncovered a 122-kb ABL1 insertion into the BCR locus (117).

Therapeutic strategies. Management of *e19a2*-positive leukemia involves sequential or combinatorial TKI regimens. Patients frequently achieve MMR through sequential use of nilotinib, dasatinib or ponatinib. Imatinib, though initially employed, is often substituted due to resistance, thrombocytopenia, fluid retention or drug interactions (119,120). Dose escalation may partially restore hematological/cytogenetic responses in resistant cases. For imatinib-resistant patients harboring the *E355G* mutation, second-generation TKIs such as nilotinib induce major cytogenetic responses, offering alternative therapeutic avenues (121). Allogeneic ASCT is utilized in select cases (122), primarily because it remains the only potentially curative treatment for CML. It becomes a critical salvage treatment option when patients develop resistance to or intolerable severe side effects from multiple TKIs, or when the disease progresses from the chronic phase to the prognostically unfavorable accelerated or blast phase.

Prognostic outcomes. The prognosis of patients with *e19a2* variant CML is influenced by genetic architecture, therapeutic regimen and individual comorbidities. Evidence indicates a trend towards favorable outcomes, but individual responses differ (119,122). While studies have linked the *e19a2* transcript to an indolent phenotype (115,123), accumulating cases demonstrate clinical courses indistinguishable from classic CML (117), with potential heightened aggressiveness (124). Second-generation TKIs such as nilotinib and dasatinib demonstrate robust efficacy, exemplified by a 72-year-old patient with chronic-phase CML who achieved CCyR at 6 months and MMR at 12 months with dasatinib combined with hydroxyurea and interferon adjuncts, underscoring its utility as frontline therapy (120). Disease progression may occur in certain cases, manifesting as leukocytosis or marrow dysplasia. Notably, a patient managed with nilotinib required dose interruptions due to grade 2 hepatotoxicity yet maintained sustained CCyR and deep MR during long-term follow-up, aligning with findings by Crampe *et al* (121) and Ernst *et al* (122), which confirmed nilotinib durable efficacy following treatment interruptions (125). Hydroxyurea monotherapy has also stabilized leukocyte counts without complications in select cases (126-128).

Resistance mechanisms pose challenges. An Italian study (118) reported a dasatinib-resistant T315I mutation, typically associated with TKI refractoriness, where dose escalation partially restored hematological and cytogenetic responses, suggesting salvage potential in mutation-positive patients. Clonal evolution, including double Ph chromosomes and tetraploidy detected via FISH and cytogenetics in an imatinib-treated patient (129), culminated in fatal blast crisis within 2 years, emphasizing the need for personalized strategies in *e19a2 BCR-ABL1*-positive CML. *e19a2* variant case reports and outcomes are summarized in Table IX.

10. e12a2 variant

The *e12a2* variant, a rare subtype, arises from fusion between e12 of the *BCR* gene and exon a2 of *ABL1*. Investigators employed primer sets (BCR-10 and ABL1-4) in RT-PCR assays to detect uncommon *e12a2 BCR-ABL1* fusion transcripts, identifying an 18-bp insertion derived from *ABL1* intron 1b at the junctional site (130). Notably, this isoform may co-occur with common transcripts, suggesting clonal heterogeneity or molecular evolution during disease progression (130).

Therapeutic approaches involve sequential TKIs (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) (130). A 59-year-old male patient with CML who developed resistance to imatinib (130) achieved CCyR and MR3 within 6 months of nilotinib escalation (800 mg/day). Due to cardiovascular adverse events, therapy was subsequently transitioned to ponatinib (15 mg/day), maintaining a MR4 for 6 years. However, management complexity arises from frequent requirement for multiple drugs, dose-limiting toxicity and treatment-associated burdens, necessitating rigorous monitoring. The paucity of reported *e12a2 BCR-ABL1* cases underscores the need for expanded cohort studies to elucidate its impact on disease progression and prognosis.

11. e18a2 variant

The *e18a2* transcript is a rare *BCR-ABL1* fusion variant arising from *t(9;22)(q34;q11)* chromosomal translocation, which juxtaposes e18 of the *BCR* gene with exon 2 *(a2)* of *ABL1*, encoding a 225 kDa fusion protein (p225) (131,132). The breakpoint within the μ-BCR region retains nearly complete BCR sequences, including calcium-binding and GTPase-Activating Protein domains specific for the Rac GTPase and coiled-coil oligomerization motifs, while preserving the intact TK domain of *ABL1* (133). The *e18a2* transcript is rare in CML, with an estimated incidence <1%. A recent study documented a 49-year-old patient with CML initially misclassified as *e19a2*-positive; relapse evaluation failed due to negative conventional RT-qPCR targeting common isoforms, highlighting diagnostic challenges (134). Coexistence of *e18a2* with *e19a2* transcripts further complicates detection (135).

Current therapeutic evidence for *e18a2* remains sparse (4,134), though insights may be extrapolated from other rare variants. In a 16-year-old female patient with CML harboring *e18a2* (136), initial RQ-PCR failed to detect the transcript, yielding false-negative results. Treatment commenced

Table VIII. Cases associated with the *e8a2* variant.

Type	Country	Age	Gender	Method	Treatment	Outcome	Follow-up duration	Diagnosis stage	Mutations	Adjustment	Transplantation	Adverse reactions	Cause of death	(Refs.)
CML Ph(+)	Uruguay	51	F	GTG-banding, FISH, RT-PCR	TKI: Imatinib, 400 mg/day. Non-TKI: Hydroxyurea	CCyR, MMR, CHR	12 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue, nausea	None	(109)
CML Ph(+)	Korea	46	M	FISH, RT-PCR	TKI: Imatinib, 400 mg/day	CHR	10 months	Chronic phase	None	No adjustment	No transplantation	Mild nausea	None	(141)
CML Ph(+)	France	43	M	RT-PCR, cytogenetic testing, FISH	TKI: Imatinib, 400 mg/day	MMR, CCyR	15 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue, GI upset	None	(116)
CML Ph(+)	China	49	M	FISH, RT-PCR, Sanger sequencing, RQ-PCR	TKI: Dasatinib, 50 mg/day. Non-TKI: Hydroxyurea, interferon	MMR, CHR	18 months	Chronic phase	None	No adjustment	No transplantation	Mild nausea	None	(110)
CML Ph(+)	Germany	74	M	RT-PCR, multiple PCR, RT-qPCR	TKI: Nilotinib, 300 mg/day. Non-TKI: Hydroxyurea	BCR-ABL1 levels are significantly decreased	24 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(108)

GTG, giemsa trypsin giemsa; FISH, fluorescence *in situ* hybridization; RT, reverse transcription; q, quantitative; TKI, tyrosine kinase inhibitor; CCyR, complete cytogenetic response; CHR, complete hematological response; NGS, next-generation sequencing; MMR, major molecular response; ddPCR, droplet digital; M, male; F, female; CML, chronic myeloid leukemia; Ph, philadelphia chromosome.

Table IX. Cases associated with the *e19a2* variant.

Type	Country	Age, years	Gender	Method	Treatment	Outcome	Follow-up duration	Diagnosis stage	Mutations	Adjustment	Transplantation	Adverse reactions	Cause of death	(Refs.)
CML Ph(+)	Italy	78	F	FISH, RT-PCR	TKI: Imatinib, 400 mg; day; nilotinib, 300 mg/day; dasatinib. 50 mg/day. Non-TKI: Interferon, cytarabine	Drug resistance	18 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(118)
CML Ph(+)	Japan	85	F	FISH, RT-PCR	TKI: Imatinib, 400 mg/day Non-TKI: Hydroxyurea	Death	12 months	Chronic phase	None	No adjustment	No transplantation	Mild nausea	Death	(129)
CML Ph(+)	Germany	89	F	FISH, RT-PCR, direct sequencing	TKI: Imatinib, 400 mg/day; dasatinib, 50 mg/day; nilotinib. 300 mg/day. Non-TKI: Hydroxyurea	No complications observed, but WBC count remained high	24 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(142)
CML Ph(+)	Tunisia	34	F	RT-PCR, FISH	TKI: Imatinib, 400 mg/day nilotinib, 300 mg/day. Non-TKI: Hydroxyurea	Initial MCyR, but TKI resistance develops later	15 months	Chronic phase	None	No adjustment	No transplantation	Mild nausea	None	(143)
CML Ph(+)	Japan	72	F	RT-qPCR, FISH	TKI: Nilotinib 300 mg/day	CCyR, MMR	18 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(129)
CML Ph(+)	Ireland	26	M	RT-PCR, Direct sequencing	TKI: Imatinib, 400 mg/day Non-TKI: Interferon, hydroxyurea therapy	e19a2 BCR-ABL1 remains	24 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(144)
CML Ph(+)	Japan	77	F	RT-qPCR,	TKI: Imatinib, 400 mg/day; nilotinib, 300 mg/day	MMR	20 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(125)

Table IX. Continued.

Type	Country	Age, years	Gender	Method	Treatment	Outcome	Follow-up duration	Diagnosis stage	Mutations	Adjustment	Transplantation	Adverse reactions	Cause of death	(Refs.)
CML Ph(+)	Ireland	53	F	Bone marrow morphology, cytogenetics, molecular analysis	TKI: Imatinib, 400 mg/day; nilotinib, 300 mg/day Non-TKI: G-CSF	MMR	24 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(121)
CML Ph(+)	Germany	33	M	Multiple PCR, Sanger sequencing	TKI: Ponatin, 45 mg/day; baxitinib, 5 mg/day. Non-TKI: Interferon	MMR	18 months	Chronic phase	None	No adjustment	No transplantation	Mild nausea	None	(122)
CML Ph(+)	France	72	F	FISH, PCR, sequencing	TKI: Imatinib, 400 mg/day; dasatinib 50 mg/day	MMR	24 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(119)
CML Ph(-)	UK	43	F	G-banded chromosome analysis, RT-qPCR	TKI: Imatinib, 400 mg/day dasatinib 50 mg/day. Non-TKI: Hydroxyurea	MMR	18 months	Chronic phase	None	No adjustment	No transplantation	Mild fatigue	None	(145)

FISH, fluorescence *in situ* hybridization; RT-PCR, reverse transcription; q, quantitative; TKI, tyrosine kinase inhibitor; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; WBC, white blood cell; CHR, complete hematologic response; NGS, next-generation sequencing; MMR, major molecular response; M, male; F, female; CML, chronic myeloid leukemia; Ph, philadelphia chromosome; dd, digital droplet.

with hydroxyurea and imatinib 600 mg/day, later decreased to 400 mg/day due to thrombocytopenia. CHR was achieved by day 56, followed by major cytogenetic response by day 106. Customized RQ-PCR monitoring revealed a decline in tumor burden to $1x10^{-3}$ by month 15. Imatinib was safely re-escalated to 600 mg/day without relapse, demonstrating favorable tolerability. The prognostic value of *e18a2* remains contentious due to limited sample sizes and undefined molecular kinetics.

12. e13a1 variant

The *e13a1* transcript is characterized by the replacement of the terminal 38 bp of *BCR* e13 with a 37-bp sequence derived from *ABL1* intron 1-2/e1, resulting in bidirectional disruption of exon junction architecture. Notably, a G>A point mutation within the inserted sequence substitutes glutamine with lysine at position 27 (137), potentially altering local charge distribution and impacting drug-binding efficiency, though direct experimental evidence remains lacking. A previous study documented a 69-year-old patient with CML initially yielding negative results with TaqMan RT-q and multiplex PCR assays; subsequent Sanger sequencing of single-step PCR products confirmed the *e13a1* transcript. The patient achieved sustained MR (*BCR-ABL1/ABL1* levels ranging from MR4.5 to MMR) following imatinib therapy, underscoring therapeutic efficacy while necessitating long-term surveillance.

13. Other variants

Certain *BCR-ABL1* transcripts reported in the literature are rare (4,61), with their clinical significance poorly defined. For example, *e1a4* and *e1a5* variants have been described exclusively in Ph^+ ALL (61), although large-scale epidemiological data validating their prevalence or clinical relevance are lacking. The *e8a4* variant was detected in a patient with Sézary syndrome (138); to the best of our knowledge, however, there have been no subsequent studies investigating this variant, and its direct association with *BCR-ABL1*-driven oncogenesis requires further exploration. The existence of these rare transcripts suggests certain variants may emerge selectively within specific disease subtypes or individuals. Nevertheless, due to limitations in detection technologies and the paucity of reported cases, numerous potential variants may remain undetected or systematically uncharacterized.

14. Discussion

The growing recognition of atypical *BCR-ABL1* fusion transcripts in CML underscores the need for nuanced diagnostic and therapeutic strategies (4,26). While canonical isoforms dominate clinical practice, atypical variants such as *e13a3, e14a3, e1a3, e1a2, e6a2* and *e8a2* exhibit distinct molecular architectures that notably influence disease biology, therapeutic responsiveness and clinical outcomes (139).

Advances in understanding atypical fusions have revealed distinct structural configurations that alter fusion protein function, dysregulating intracellular signaling, proliferation, differentiation and apoptosis. Therapeutic strategies combining TKIs, chemotherapy and ASCT demonstrate variable efficacy across subtypes. While certain patients achieve durable remission, others experience refractory disease or rapid progression, highlighting pronounced inter-variant prognostic heterogeneity. For example, *e13a3* and *e8a2* variants are frequently associated with indolent disease course and favorable responses to TKIs, as evidenced by sustained cytogenetic and molecular remissions in multiple case series (7,44,110,116). Conversely, patients with *e1a2* and *e6a2* isoforms experience more rapid disease progression, including accelerated phase or blast crisis. In refractory cases, 5-year OS rates are 40-70%. Notably, patients with *e1a2*-positive CML often present with lymphoid blast crisis-like features, including monocytosis and absence of basophilia, mirroring Ph-positive ALL. Similarly, *e6a2* cases show elevated rates of clonal evolution and resistance mutations, necessitating early escalation to second-generation TKIs or ASCT. These findings emphasize that atypical transcripts are not uniformly benign and require vigilant monitoring. TKI responsiveness varies significantly across atypical variants. While imatinib remains effective for *e13a3* and *e8a2*, *e1a2* and *e6a2* subtypes often require early transition to second- or third-generation TKIs due to intrinsic resistance. Dose adjustments or combination regimens may salvage responses in resistant cases, as demonstrated in patients with *e6a2* achieving molecular remission post-ASCT. However, therapeutic decisions must balance efficacy against toxicity, particularly in elderly or comorbid populations. For example, dose reduction mitigates hepatotoxicity while maintaining remission in *e14a3* cases.

Conventional diagnostic methods, such as standard RT-PCR or FISH, may fail to detect rare fusion isoforms due to primer mismatches or cryptic chromosomal rearrangements. For example, *e1a3* and *e6a2* transcripts are frequently missed by routine assays, leading to delayed diagnosis and inappropriate therapeutic choices. Complementary techniques, including multiplex RT-PCR, nested PCR and RNA-seq, are essential for identifying atypical breakpoints and coexisting mutations that may drive disease progression. ddPCR further enhances sensitivity for minimal residual disease monitoring, particularly for low-abundance transcripts such as *e6a2*.

Data on atypical transcripts derive predominantly from case reports and small cohorts, limiting statistical power and generalizability. To address these challenges, multicenter collaborative studies are required to expand case accrual and establish robust genomic databases. Mechanistic investigations should delineate molecular pathways and crosstalk between atypical fusions and ancillary signaling networks, informing precision therapeutics. Diagnostic innovation should prioritize high-sensitivity/specificity assays for rare fusion detection, enabling early intervention. Therapeutic development requires variant-tailored approaches integrating genomic profiling, disease stage and patient comorbidities, alongside intensified research into resistance mechanisms and salvage strategies. Longitudinal studies assessing long-term outcomes and survivorship are key to optimize holistic care, refine prognostic stratification and ultimately improve survival for patients with atypical *BCR-ABL1*-positive leukemia.

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Authors' contributions

XZ wrote the manuscript and constructed figures and tables. AL, DK and PZ revised the manuscript. YS and NS designed the methodology. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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