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Prognostic factors in chronic myeloid leukemia: at diagnosis and for treatment-free remission

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Prognostic factors in CML

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Abstract

Although chronic myeloid leukemia (CML) is defined by the sole presence of the *BCR::ABL1* fusion gene—the genetic event underlying the genesis of the disease—the diversity of clinical outcomes, even in the tyrosine kinase inhibitors (TKI) era, reveals that its apparent biological homogeneity is, in fact, misleading, both between and within individuals. Increasing knowledge of biological diversity through advances in cellular analytical tools and expansion of the TKI arsenal to address this heterogeneity are key factors in the path to a better disease control and ultimately cure.

In this review, we focus on well-established and novel modifiable and non-modifiable prognostic factors of CML at diagnosis and for treatment-free remission, with particular emphasis on those that are easy to use in clinical practice. We will discuss how these factors may help shape therapeutic choices. Finally, we will highlight innovative research avenues aiming at improving prognostication of CML.

Introduction

Chronic myeloid leukemia (CML) was the first neoplasm found to be associated with a recurrent acquired cytogenetic abnormality in hematopoietic stem cells: the Philadelphia chromosome (Ph1). Ph1 results from the reciprocal t(9;22)(q34;q11) translocation, leading to the formation of the *BCR::ABL1* hybrid gene, the primary driver of the disease.[1]

The discovery of imatinib, which targets the ATP binding site of the aberrantly activated BCR::ABL1 oncoprotein, pioneered the use of tyrosine kinase inhibitors (TKIs) in cancer therapy. Imatinib revolutionized the treatment and prognosis of CML patients. After its first approval in 2001, 2nd and 3rd generation of ATP-competitive TKIs were developed to overcome imatinib weaknesses[1]. These agents exhibited greater inhibitory potency towards native BCR::ABL1 and the capacity to fight a wide array of kinase domain (KD) mutant forms. In recent years, allosteric inhibitors of BCR::ABL1 joined the therapeutic arsenal with asciminib as the lead agent. These compounds offer greater selectivity, potentially translating into improved drug safety and quality of life[2].

With such an impressive therapeutic arsenal to fight CML, relative survival rates at chronic phase (CP)-CML diagnosis have reached remarkably high levels. Patients exhibit a quite small excess mortality relative to the general population, providing TKI availability, proper management and treatment adherence. Progression to blast crisis occurs in only about 2 to 5% of patients annually during the first 2 years and 10-year estimates of freedom from progression range between 90 and 95%[3]. With such apparent remarkable outcome in CML, why should one remain interested in prognostic and predictive systems? Even with the remarkable success of TKIs, prognostication remains essential as CML is a heterogeneous disease both clinically and biologically. CML may emerge on a normal or an altered hematopoietic background, present asymptomatically, with mild or severe inaugural symptoms. The disease may remain in chronic phase or progress through accelerated or blast phase in a bi or triphasic manner. In addition to Ph1, other cytogenetic abnormalities and a broad spectrum of somatic mutations may be present, reflecting underlying sub clonal diversity. In the chronic phase of the disease, outcomes may range from progression to treatment-free remission (TFR).

In this review, we will describe the well-established prognostic factors of CML-specific survival and progression-free survival (PFS) at diagnosis and discuss how these factors guide therapy and shape monitoring strategies. We will also examine the predictors for

TFR eligibility and success. Finally, we will highlight ongoing research and novel strategies to improve prognostication.

Evolving definition and importance of CML phases at diagnosis

CML is classically divided into three phases - chronic, accelerated, and blast - based on the natural evolution of the disease. These phases are defined by cytological features in the peripheral blood, bone marrow and potentially involved extra-medullary sites. Whether present at diagnosis or occurring on-therapy, findings of acceleration represent a warning to blast crisis development. Blast crisis whether myeloid, lymphoid or of mixed phenotype carries a very poor prognosis and requires combination therapy followed by allogeneic stem cell transplantation[4,5]. Thus, proper recognition of CML phases is essential for selection of the most appropriate treatment strategy (Table 1). Several classification systems of CML phases exist including those proposed by the World Health Organization (WHO) and the International Consensus Classification of Myeloid Neoplasms and Acute Leukemia (ICC)[6,7]. WHO challenges the existence of an accelerated phase and instead considers acceleration as a CP with high-risk features. Blast phase is defined by the presence of at least 20% of blasts. ICC retains acceleration in case of 10 to 19% of blasts or at least 20% basophils, blast phase is defined by the presence of at least 20% of blasts or at least 5% of morphologically identifiable lymphoid blasts or a chloroma made of blast cells. Patients diagnosed with *de novo* disease acceleration should receive the most potent approved TKI upfront, namely a 2nd generation ATP competitive TKI; allosteric TKIs have not yet been evaluated in this context[8-9].

Within the blast phase category whether occurring *de novo* or on-therapy, diagnostic and prognostic factors are important to recognize and should include at least immunophenotyping, karyotyping and *BCR::ABL1* mutation analysis (Table 1). Targeted Next Generation Sequencing (NGS) panel assessment to identify commonly mutated myeloid or lymphoid genes, although experimental, may help identifying targetable abnormalities other than *BCR::ABL1*.

Prognostic factors and risk stratification in CP- CML at diagnosis

Clinical and cytological grading: the Eutos Long Term Survival Score

The Eutos Long Term Survival (ELTS) score was established in 2016. ELTS was developed using a European cohort of adult patients treated with first-line imatinib. The goal

was to provide a more accurate estimate of the risk of dying from CML compared to traditional scores elaborated, such as the Sokal score[10]. The risk of death was calculated from the time of diagnosis. In the ELTS score model, death from CML was defined as death after progression to advanced phases. This definition did not take into account death possibly attributed to CML complications in CP - for example as a consequence of leukostasis - nor did it include indirect deaths such as those due to therapy-related complications. The parameters included in the ELTS score calculation are age, spleen size below costal margin, peripheral blasts and platelet counts. The score segregates patients into 3 categories: low (62% of patients), intermediate (27% of patients) and high risk (12% of patients) with respective 8-year probabilities of dying from CML of 2%, 6% and 11%. Based on these findings, the National Comprehensive Cancer Network (NCCN) recommends the use of 2nd generation or allosteric TKIs upfront in intermediate or high-risk patients rather than imatinib and the European LeukemiaNet (ELN) acknowledges that a high ELTS score may warrant the use of a more potent TKI than imatinib as initial therapy (Table 1)[8,11]. Low-risk patients may also benefit from potent TKI upfront in terms of likelihood of TFR eligibility due to a higher incidence of DMR than with imatinib[12].

Additional chromosome abnormalities

At the time of CML diagnosis, bone marrow karyotyping is essential. In approximately 99% of cases, Ph1 is detectable, either isolated, as part of a variant translocation or together with additional chromosomal abnormalities (ACA). The prognostic influence of complex variant translocations during TKI treatment is unclear[13]. ACA may be present in 5 to 10% of newly diagnosed CP-CML cases with rising proportions in advanced phases of the disease, suggesting genetic instability. ACA are categorized into 3 groups based on their frequency: major route, minor route and rare[14]. Prognostic implications of ACA at CP-CML diagnosis were retrospectively studied in a German cohort of adult patients treated with first-line imatinib and in a British study with adult patients randomized to receive either imatinib or dasatinib[15,16]. Overall in both studies, the presence of ACA at diagnosis was associated with poorer PFS or freedom from progression, regardless of the ELTS score (Table 1). Worse prognosis was seen with complex karyotypes and the following major and minor route abnormalities: +8, +Ph1, i(17q), +19, +17, +21, -7/7q-, 3q26 and 11p23[17]. However, within this high-risk group, the prognostic weight of individual ACA differs. 3q26, 11p23, i(17q) and -7/7q- rearrangements and complex karyotypes confer a much unfavorable prognosis than

isolated +8 or +Ph1[18,19]. From a therapeutic standpoint, there is no clear guidance on the optimal treatment approach in case of ACA as comparative studies are lacking and owing to the small number of cases. 3q23.2 rearrangements involving *MECOM* or overexpression of the oncogenic transcription factor *EVI1* might require 3rd generation TKI although not approved upfront, followed by allogeneic stem cell transplantation due to high risk of resistance and progression to blast crisis[20].

BCR::ABL1 transcripts subtypes

The chromosomal breakpoints in the *BCR* and *ABL1* genes are variable, leading to 2 major fusion transcripts and at least 7 different atypical transcripts[21]. The major transcripts e13a2 and e14a2 encode for a 210kD BCR::ABL1 protein and account for 95% of the cases. The remaining cases include the minor e1a2 and the micro e19a2 transcripts, translating into a 190kD and a 230kD BCR::ABL1, respectively, and other very rare transcripts. Whether these different molecular rearrangements and corresponding BCR::ABL1 proteins may be associated with specific clinical and biological features of prognostic significance is an important question.

In some retrospective observational studies comparing outcomes of patients with either of the major transcripts, there was a trend towards a greater probability to reach optimal cytogenetic and molecular responses during 1st line imatinib or 2nd generation TKI therapy when e14a2 was present[22]. Some even report a slightly higher TFR rate in patients carrying the e14a2 transcript[23,24]. However, findings from other studies conducted after adjustment for additional prognostic factors challenged these observations and concluded that although e13a2 and e14a2 encoded a p210 BCR::ABL1 protein differing by 25 amino acids, these were not biologically distinct enough to substantially influence clinical outcomes[25,26]. Furthermore, biologists underlined that current real time (RT)-quantitative polymerase chain reaction (qPCR) techniques slightly overestimated the e13a2 transcript burden, suggesting that differences in molecular responses between patients carrying e13a2 or e14a2 transcripts may result in part from a technical reason[29]. The use of droplet digital PCR instead of RT-qPCR may help solving this issue[29]. At present, it is reasonable to consider that the 2 major transcript types are neither regarded as relevant prognostic factors nor a basis for selecting different TKIs, unlike rare transcripts.

Rare transcripts lacking *ABL1* exon a2 sequences such as e13a3, e14a3 or e1a3 constitute a contraindication to the use of allosteric inhibitors (Table 1). Indeed, exon a2

encode part of the SH3 domain of BCR::ABL1, and lack of an intact SH3 domain confers resistance to allosteric inhibitors such as asciminib[30,31]. The rare e1a2 fusion, which results in the p190 BCR::ABL1 protein and is one of the most prevalent uncommon transcripts worldwide, is considered a high-risk feature at diagnosis (Table 1). It is associated with poorer treatment responses and a higher risk of progression on ATP-competitive TKIs, particularly imatinib, compared to major transcripts[32,33]. The biological basis for the aggressiveness of p190 BCR::ABL1+ CML includes its higher kinase activity and the activation of distinct signaling pathways compared to p210 BCR::ABL1[34]. The e19a2 transcripts associated with p230 BCR::ABL1+ CML was historically considered as an indolent disease due to a mild clinical presentation and natural evolution[35]. This belief was later contradicted by a high risk of resistance to imatinib and a low success rate of TFR[36,37]. Altogether, these findings suggest that the most potent TKIs, such as second-generation ATP-competitive TKIs, might be considered upfront for patients with rare transcript variants.

Pre-existing BCR::ABL1 point mutations

The emergence of *ABL1* point mutations within the KD and the neighboring linker, SH2, SH3, and Cap domains is a well-established mechanism of resistance to TKIs, impairing or abolishing drug ability to bind to and/or inactivate the oncoprotein[38]. A key question is whether these mutations pre-exist within the leukemic clone at low frequencies or arise *de novo* because of a selective pressure exerted by TKI therapy. In fact, evidence suggests that both phenomena may coexist. Historical studies conducted prior to the next-generation sequencing (NGS) era and involving a limited number of patients demonstrated that mutated leukemic cells were present prior to exposure to TKI treatment[39-42]. However, no clear correlation was found with response to ATP-competitive TKI or survival[41]. Although the true frequency of *ABL1* KD point mutations at CML diagnosis remains unknown with the use of highly sensitive techniques such as NGS or single-cell sequencing and despite the uncertain impact of such pre-existing mutations on responses to allosteric TKIs, current guidelines do not recommend *ABL1* mutational screening at diagnosis, as it is not considered a criterion for TKI selection[29,43].

Genomic alterations outside the BCR::ABL1 gene

CML was historically considered a genetically uniform disease due to the presence of the *BCR::ABL1* rearrangement, the hallmark of the disease, however this view is outdated. Initial evidence of the molecular heterogeneity in CML at diagnosis was documented in 2005 in a patient carrying a missense *RUNX1* heterozygous mutation within the *BCR::ABL1*$^{+}$ clone[44]. The patient progressed to myeloid blast crisis while on imatinib with blast phase clone harboring the same *RUNX1* mutation, as well as trisomy 21 and a *BCR::ABL1* M244V point mutation. With remarkable advances in sequencing technologies and analytical tools, the interest in deciphering additional genomic abnormalities in CP-CML at diagnosis is growing, to uncover their potential prognostic significance and to understand their dynamics during TKI treatment. Genetic profiling with varying methodological and technological approaches such as targeted NGS analysis using panels of genes commonly mutated in myeloid malignancies or whole-exome or transcriptome sequencing (WES/WTS RNA-Seq) was first performed in selected patient populations poorly responding to TKI or progressing to advanced phase. The most frequently altered genes in diagnostic or follow-up samples, apart from *BCR::ABL1*, were the transcription factor *RUNX1*, the epigenetic regulators *ASXL1*, *TET2* and *DNMT3A*, and the tumor suppressors *IKZF1*, *TP53* and *BCORL1*, suggesting an adverse clinical impact of some of these alterations[45-50]. Studies in less or unselected series of patients with newly diagnosed CP-CML have also been performed or are ongoing. Overall, genomic alterations outside of *BCR::ABL1* are observed in approximately 20-30% of CML patients at diagnosis, with *ASXL1* mutations being the most commonly encountered[51-55]. Most studies report a correlation between these somatic variants, especially *ASXL1*, and non-optimal molecular responses including failure, emergence of *BCR::ABL1* mutations, and disease progression[56]. Currently, the incorporation of somatic variants as baseline prognostic molecular signature remains premature in routine practice for several reasons[8,29]. First, there is no consensus on the optimal technique or relevant gene panel to be used. Second, larger cohorts of unselected patients, ideally through international collaboration, will be required to more precisely determine the prognostic value of somatic variants and in case of clonal hematopoiesis of indeterminate potential (CHIP), the risk of a second hematological malignancy. Third, technical improvements—particularly in the sensitivity for detecting and monitoring mutated clones—are needed to properly assess on-treatment dynamics. Fourth, the current state of the art is insufficient to provide reliable guidance for treatment selection.

Prognostic and predictive factors of treatment-free remission

Long-term on-treatment PFS is not the sole therapeutic goal in CML management. Indeed, some patients can discontinue TKI therapy without experiencing hematological relapse despite evidence of *BCR::ABL1*+ cells in most of them, a condition known as TFR[57]. The requirements for stopping therapy with a fair chance of success differ from those necessary to optimally prevent progression to advanced-phase disease. Indeed, achieving only a 3-log reduction in *BCR::ABL1* transcript levels makes the likelihood of achieving TFR quite low. A threshold of at least a 4-log (MR4) is generally required to provide a reasonable chance—not less than 50%—of success[58]. Once a DMR is achieved, it is important to continue therapy for an additional 2 to 3 years at least, as the risk of early relapse following treatment discontinuation is a time-dependent variable. This likely reflects long-term effects of therapy, though the underlying mechanisms are not fully understood. The ELN has empirically defined criteria considered reasonable for TKI discontinuation as follows: (1) duration of TKI therapy of at least 5 years if imatinib and 4 years if 2nd generation ATP-competitive TKIs, (2) duration of DMR of at least 4 years if MR4 and 2 years if MR4.5 (Table 2)[8].

While it is tempting to predict the likelihood of achieving TFR from the time of diagnosis, this remains an unrealistic goal. Current models do not adequately account for how TKIs influence clonal heterogeneity and the leukemic microenvironment over time, nor how they modulate the impact of baseline disease characteristics. Nevertheless, treatment strategies can be optimized at diagnosis to maximize the likelihood of reaching DMR levels.

Factors underlying deep molecular response achievements

There is strong evidence that the probability to achieve a DMR is influenced by at least 3 factors: CP-CML characteristics at diagnosis, TKI potency and MR category during the first year of treatment. The phase 3 randomized trial ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients) demonstrated that patients with a high Sokal score at diagnosis had a lower probability to obtain DMR than patients with an intermediate or low risk score, regardless of whether a 1st or a 2nd generation TKI was used[59]. The 5-year cumulative incidence of MR4.5 was 44.9% in high-risk patients and 60.4% and 53.4% in intermediate or low risk patients receiving frontline nilotinib. ENESTnd also showed that when imatinib was given upfront, DMR probabilities were lower than in nilotinib-treated patients, regardless of the Sokal score. The 5-year cumulative incidence of MR4.5 was 23.3% in high-risk patients and 32.7 and 36.5% in intermediate or low risk

patients receiving frontline imatinib. The superiority of 2nd generation ATP-competitive TKI over imatinib was confirmed with dasatinib in the DASISION trial and bosutinib in the BFORE study[60,61]. Importantly, both dasatinib or nilotinib demonstrated comparable efficacy in achieving DMR[62]. Frontline therapy is currently expanding with the advent of allosteric inhibitors such as asciminib but data are too preliminary to predict a definitive advantage in achieving DMR over 2nd generation TKIs[63].

Once treatment has started, there is evidence that molecular responses obtained within specific timeframes during the first 12 to 24 months of treatment may serve as meaningful surrogate markers of DMR achievement at later time points. In the DASISION trial, early molecular responses (EMR) at 3 months (*BCR::ABL1* < 10% IS) were obtained in 64% of imatinib-treated patients and 84% of dasatinib-treated patients and respective MR4.5 probabilities at 5 years were 48% and 54%. In sharp contrast, patients lacking EMR representing 36% of those treated with imatinib and 16% of those receiving dasatinib, achieved MR4.5 by 5 years in only 12 and 5% of the cases, respectively[60]. Sasaki et al retrospectively attempted to determine which molecular milestones during the first 12 months of TKI best predicted longer-term DMR[64]. They found that the optimal MRD levels to achieve stable MR4.5 were 0.051%, 0.019%, 0.007%, and 0.003% IS at 3, 6, 9, and 12 months, respectively. The clinical usefulness of early therapeutic intervention in patients lacking this level of response remains unknown.

Factors underlying treatment-free remission or relapse

When patients meet reasonable criteria for stopping therapy, the probability of successful TFR ranges from 50% to 70%. Those in whom *BCR::ABL1* transcripts increase above the 3-log threshold (0.1% IS or MMR) are considered as relapsing patients and are instructed to restart therapy. Most molecular relapses—approximately 85 to 90%—occur within the first six months after treatment discontinuation and progress with very rapid kinetics, whereas the remaining late relapses emerge more gradually, suggesting underlying biological differences[65]. Dramatic events, such as progression to blast crisis during the treatment-free phase, cannot be entirely ruled out but are fortunately very rare[66,67]. Patients who maintain MMR without any treatment are generally considered to be functionally cured but require lifelong monitoring.

From a clinical perspective, it would be valuable to have simple and reliable tools to predict individual patient outcome upon TKI discontinuation to better guide the decision-

making process. Efforts to create predictive scoring systems or to integrate kinetics of *BCR::ABL1* decline early after TKI initiation have not achieved widespread routine use but there are several simple parameters that may help estimating the likelihood of success or failure in achieving TFR: the depth of DMR, the duration of DMR, the ability to maintain DMR upon de-escalation of TKI therapy and the residual disease levels early after TKI discontinuation (Table 3). Although detectability of MRD in patients achieving MR4 or MR4.5 do not preclude TKI discontinuation, some studies suggest that the deeper responses are, the higher the likelihood of TFR may be[68,69]. In the JALSG-STIM213 trial, 3-year TFR was 35.7% in patients who stopped imatinib in stable but detectable MR4.5 and 72.2 % in those with undetectable MRD[68]. The multicenter international EUROSKI trial demonstrated that DMR duration prior to imatinib discontinuation was a prognostic factor of early but not late molecular relapses and each additional year in DMR was associated with a probability increase of around 3% to maintain MMR at 6 months[70]. TKI treatment duration was also an important parameter of success in the pioneering STIM trial[71]. Whether this holds true for patients treated with more potent TKIs, such as 2nd and 3rd generation TKI or allosteric drugs remain to be determined. Analyzing the impact of gradual de-escalation of TKI therapy before TKI discontinuation on TFR rates is of great clinical interest and is currently being investigated in several prospective studies. The underlying hypothesis of these investigations is that the ability to maintain a DMR on a low dose TKI may help identify patients with low risk of relapse after TKI discontinuation[72,73]. Finally, the behavior of MRD early after TKI discontinuation is a great indicator of outcome as demonstrated in the STOP2G trial were loss of MR4.5 3 months after stopping TKI was predictive of failure to maintain MMR later on[74]. Lineage-specific assessment of peripheral blood MRD just before treatment discontinuation is currently being explored as a mean to improve TFR prediction, as well as presence of *BCR::ABL1* DNA *versus* RNA in residual leukemic cells and age-related clonal hematopoiesis[75-77].

From a scientific standpoint, if we admit that leukemic stem cells (LSC) persist in all patients even in those in DMR, understanding the biological mechanisms underlying TFR or relapse is a challenging but key objective for future prospect. Multiple independent studies have shown a strong relationship between natural killer cells, immune suppressors, and TFR[78-80]. However, attempts to increase eligibility to or rates of TFR through immune stimulation with interferon alpha or immunomodulatory antibodies have so far failed to yield meaningful results[81,82]. There is also a high interest in trying to understand how the bone marrow microenvironment or even TKIs protect LSC from eradication to try building

strategies to overcome this barrier[83]. Finally at the LSC level, research is ongoing to better understand their inter and intra individual heterogeneity[84,85]. Altogether, the goal is not only to increase functional cure but also to reach eradication cure, in which LSC are fully eliminated.

Conclusion

Classical clinical and cytological prognostic factors of CML at diagnosis remain relevant in the TKI era and impact treatment choices as the panel of drugs is in continuous expansion. However, these are not sufficient for an accurate stratification of the disease risk. ACA, although rather infrequent, are to be taken into consideration. High-risk ACA do not completely overlap with the most frequent major ones and explorations to provide the complete catalog of worrying abnormalities are still necessary. The advent of allosteric TKI has triggered a regain of interest in transcript typing due to their inability to inactivate BCR::ABL1 isoforms lacking regions encoded by the exon 2. Transcript types also play a key prognostic role as the varying corresponding BCR::ABL1 proteins may not possess the same oncogenic properties and interaction with TKIs may differ. Considerable efforts are ongoing to understand the cellular and molecular heterogeneity of CML apart from the *BCR::ABL1* rearrangement but there are some technical hurdles to their application in clinical practice and we lack a dynamic view on how baseline heterogeneity evolves during therapy. Finally, although CML-specific survival and TFR share some common prognostic factors, an accurate prognostic scoring system for TFR is lacking at diagnosis. In TFR eligible patients, decision to stop therapy relies on common sense. Investing in research aiming at understanding complex interaction between LSC, the bone marrow niche ecosystem and TKI is more than ever necessary.

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Table 1: Key prognostic parameters at baseline

Item	Clinicobiological importance	Impact on management
CML phase (Blood and marrow cytology)	Prognostic value: survival	More potent TKI if accelerated phase Combination therapy +/- allogeneic SCT if blast phase
ELTS or Sokal score	Prognostic value: death from CML	More potent TKI preferred if high-risk group
Cytogenetic characteristics	Prognostic value: responses	More potent TKI if high-risk ACA or Ph1 duplication
Immunophenotype	Distinguishes myeloid from lymphoid blasts in BC	Key parameter for treatment choices in blast crisis
***BCR ::ABL1* transcript type**	Prognostic value: responses Monitoring implications	E1a2 might require potent TKI No allosteric TKI in case of a3-containing transcript
***BCR::ABL1* point mutations**	No prognostic value in CP	None at diagnosis in CP
Genomic characteristics	Likely yes (e.g. *ASXL1* alterations in CP)	Not yet

Table 2: Clinical and biological parameters impacting the TKI discontinuation decision-making process in daily practice

Parameter	Condition for TKI discontinuation	Impact on TFR success rate
TKI treatment duration	Not less than 3 years At least 5 years if imatinib At least 4 years if more potent TKI	Yes
Molecular response level ≥ MR4 vs < MR4	Not less than a MR4	Yes
DMR duration	Not less than 2 years	Yes

Table 3: Biomarkers influencing treatment-free remission but without improvement in clinical-decision making

Item	Positive parameters	Negative parameters
Diagnostic features	*E14a2* transcript	E19a2 transcript High ELTS or Sokal score
Response to therapy	Short *BCR::ABL1* halving time MR deeper than MR4 DMR maintenance after TKI de-escalation	DMR after warning/resistance
***BCR::ABL1* DNA localization**	Absent in granulocytes and lymphocytes	Present in granulocytes
Genomic profiling at discontinuation	Age-related clonal hematopoiesis	Unknown
Immune environment	Cytotoxic NK cells	Regulatory T-cells T-cell suppressors