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ORIGINAL REPORT

Impact of Treatment End Point Definitions on Perceived Differences in Long-Term Outcome With Tyrosine Kinase Inhibitor Therapy in Chronic Myeloid Leukemia

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ABSTRACT

Purpose
Different definitions of progression-free survival (PFS) and event-free survival (EFS) may result in perceived differences in outcomes with tyrosine kinase inhibitor (TKI) therapies in chronic myelogenous leukemia (CML).

Patients and Methods
We analyzed the outcome of 435 patients with early chronic-phase, Philadelphia chromosome–positive CML treated with imatinib (n = 281), nilotinib (n = 78), and dasatinib (n = 76) using definitions of PFS and EFS used in the International Randomized Study of Interferon Versus STI571 (IRIS), Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENEST-nd), Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients (DASISION), and MD Anderson Cancer Center (MDACC) trials. Definitions for EFS-IRIS, time without progression in ENEST-nd, PFS-DASISION, and EFS-MDACC were as previously reported. The EFS-MDACC considered an event any instance of toxicity or death from any cause on or off therapy (if not counted before death as progression/event).

Results
Of the 435 patients, 123 (28%) were taken off TKI therapy (resistance/loss of response, n = 33; blastic phase on TKI therapy, n = 6; intolerance/toxicity, n = 29; other causes, n = 55). Thirty-three patients (7.6%) have died; eight patients died on TKI therapy, two patients died within 60 days of being off TKIs, and 23 patients died after being off TKIs for more than 60 days. Of the 33 deaths, 19 deaths (eight deaths on TKI, two deaths within 60 days, and nine deaths off for resistance/relapse/transformation) would be counted as progression/events on the IRIS/ENEST-nd/DASISION studies, whereas 14 deaths would be censored at time off TKI. On the basis of the four definitions used by IRIS, ENEST-nd, DASISION, and MDACC trials, the corresponding 5-year PFS/EFS rates were 96%, 90%, 89%, and 81%.

Conclusion
Uniform definitions of PFS and EFS are needed to compare the long-term efficacy and potential use of different TKIs in CML.

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INTRODUCTION

The Bcr-Abl tyrosine kinase inhibitors (TKIs) have revolutionized the treatment and prognosis of chronic myeloid leukemia (CML).[1-3] Early surrogate end points of long-term prognosis in CML include the achievement of complete cytogenetic response (CCyR) and the achievement of major molecular response (MMR) in the first 12 to 18 months.[4-6] Long-term prognosis is measured by several end points, including overall survival, progression-free survival (PFS), and event-free survival (EFS).

Imatinib mesylate is an established front-line standard therapy in CML.[7] The success of second-generation TKIs in CML after imatinib treatment failure[8-10] resulted in their evaluation in front-line CML therapy.[11,12] Compared with imatinib, second-generation TKIs, such as nilotinib and dasatinib, have been associated with higher rates of CCyR and MMR at 12 to 18 months, lower incidences of progression to the accelerated phase (AP) and blastic phase (BP) of CML, and, on average, better toxicity profiles. The favorable results achieved with second-generation TKIs establish them as new standards of care in front-line CML therapy. Imatinib may become available in generic formulations within the next 5 years at a significantly lower cost. The choice of front-line

TKI therapy may then be influenced by the differences in long-term outcomes.

The estimated 7- to 10-year survival in patients with newly diagnosed CML with imatinib therapy is 85% to 90%, but is 93% to 95% if only CML-associated deaths are considered.[3,13] To demonstrate significant differences in survival at 7 to 10 years will require large numbers of patients. Even then, the survival difference with second-generation TKIs versus imatinib may not be significant enough to justify the difference in costs of therapy for the total population with CML. Therefore, other end points of long-term outcome, such as PFS and EFS, become important.

Different definitions of progression and event are used in different studies of CML. The definitions most frequently used are derived from the International Randomized Study of Interferon Versus STI571 (IRIS). In this study, what was first called progression[1] was later considered an event,[7] further confusing measurements of PFS and EFS. Differences in these definitions may result in perceived but not real differences in outcomes when comparing different TKIs or outcomes on different studies. In addition, in multi-institutional trial designs, patients may be taken off study for occurrences other than progression or an event, such as toxicity, intolerance, patient request, or other causes. Such patients are sometimes censored at the time they are taken off TKI therapy, and their subsequent CML progression is not captured beyond 30 to 60 days after discontinuation of TKIs. This is because of the limited capacities of such trials to observe patients after 30 to 60 days off TKI and the trial design, which does not allow for such follow-ups (except for death). Also, once patients are off the protocol TKI, they cannot be precisely evaluated for progression because marrow and cytogenetic studies may not be performed or allowed to be captured in the subsequent course of patients on the particular TKI protocol. These calculations assume that these events/progressions are not influenced anymore by the TKI treatment, which has been discontinued. Single-institution studies are better suited to monitor all patients for progression or events even after they are taken off the particular protocol TKI.

The aim of this study is to analyze the impact on patient outcome of differences in the definitions of PFS and EFS, as used in large-scale randomized trials (ie, IRIS, Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients [ENEST-nd], and Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients [DASISION]) and in MD Anderson Cancer Center (MDACC) trials of patients with newly diagnosed CML receiving TKIs. Significant differences in the perceived outcomes, when using different definitions of PFS and EFS, may alert to the need for uniform definitions of long-term prognosis in CML.

PATIENTS AND METHODS

From July 2000 until April 2010, 435 patients with newly diagnosed Philadelphia chromosome (Ph) –positive CML in chronic phase (CP) were treated with imatinib (n = 281), nilotinib (n = 78), and dasatinib (n = 76) within 12 months from diagnosis. These patients were treated on the following front-line CML protocols available during the time period at our institution: imatinib from July 2000 until July 2005,[14,15] nilotinib from July 2005 until April 2010, and dasatinib from November 2005 until April 2010.[16,17] Patients with clonal evolution without other accelerated features were included. All patients were included in this analysis for their long-term outcome, including overall survival, PFS, and EFS. Survival probabilities were estimated using the Kaplan-Meir method.

Different definitions, as published in previous studies, were used. The definition of EFS on the IRIS trial referred to an event as any of the following: progression to AP or BP on imatinib; death as a result of any cause on imatinib; or loss of complete hematologic response (CHR) or major cytogenetic response (MCyR).[7] The definition of time without progression by ENEST-nd referred to progression as any of the following: development of AP or BP on nilotinib or imatinib therapy or CML-related death on nilotinib or imatinib therapy or within 30 days off TKI therapy.[12] The definition of PFS on DASISION referred to progression as any of the following: progression to AP or BP on imatinib or dasatinib; death as a result of any cause on imatinib or dasatinib; loss of CHR or MCyR on imatinib or dasatinib; or an increase in WBC count to more than 20×10^9/L on imatinib or dasatinib. Death was coded on imatinib or dasatinib therapy and within 60 days off TKI therapy.[11] The definition of EFS in the MDACC studies referred to an event as any of the following: progression to AP or BP; loss of MCyR; hematologic resistance including loss of CHR or lack of achievement of response by the European Leukemia Network criteria; being taken off TKI therapy for any toxicity; or death from any cause (whether CML related or not) whether the patient is on or off TKI therapy (if no previous events were accounted for as event or progression before death).[14] Table 1 lists these definitions.

Because salvage therapies after front-line TKI therapy exist that are effective, it may be argued that the only two important events relevant to prognosis of patients with CML are progression to BP or death from any cause. A new definition of long-term outcome, survival without BP, was used as a long-term end point in CML.

Table 1. Definitions of PFS, EFS, and TWP in Different Studies

Occurrence	EFS-IRIS	TWP-ENEST-nd	PFS-DASISION	EFS-MDACC*
AP-BP				
On TKI	+	+	+	+
Off TKI	–	–	–	+
Death				
On TKI	+	CML related	Any cause	+
Off TKI	–	CML related < 30 days off TKI	< 60 days off TKI	+
Loss of CHR/MCyR	+	–	+ (also ↑WBC)	+

NOTE. Plus sign (+) means included as an event; minus sign (–) means not included.

Abbreviations: AP, accelerated phase; BP, blastic phase; CHR, complete hematologic response; CML, chronic myeloid leukemia; DASISION, Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients; EFS, event-free survival; ENEST-nd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients; IRIS, International Randomized Study of Interferon Versus STI571; MCyR, major cytogenetic response; MDACC, MD Anderson Cancer Center; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TWP, time without progression.

*EFS-MDACC accounts for any event off TKI and any death on or off TKI, as well as lack of response on the basis of the European Leukemia Network criteria.

Table 2. Demographics and Clinical Characteristics of Study Group (N = 435)

Demographic or Clinical Characteristic	No. of Patients	%
Age, years		
Median	48	
Range	15-85	
≥ 60	95	22
Female	179	41
Sokal risk score		
Low	300	69
Intermediate	106	24
High	29	7
Hemoglobin, g/dL		
Median	12.3	
Range	6.2-16.7	
< 12	180	41
WBC count, $\times 10^9$/L		
Median	27.4	
Range	0.8-342.5	
> 50	142	33
Platelet count, $\times 10^9$/L		
Median	337	
Range	58-2,000	
> 450	133	31
Cytogenetic clonal evolution (n = 432)	20	5
Prior therapy		
None	226	52
Hydroxyurea	151	35
Other	58	13
Imatinib for < 1 month	54	
Interferon for < 1 month	4	
Front-line CML therapy		
Imatinib*	281	65
Nilotinib	78	18
Dasatinib	76	17

Abbreviation: CML, chronic myeloid leukemia.
*Two hundred eight of 281 patients received an initial imatinib dose of 400 mg orally twice daily.

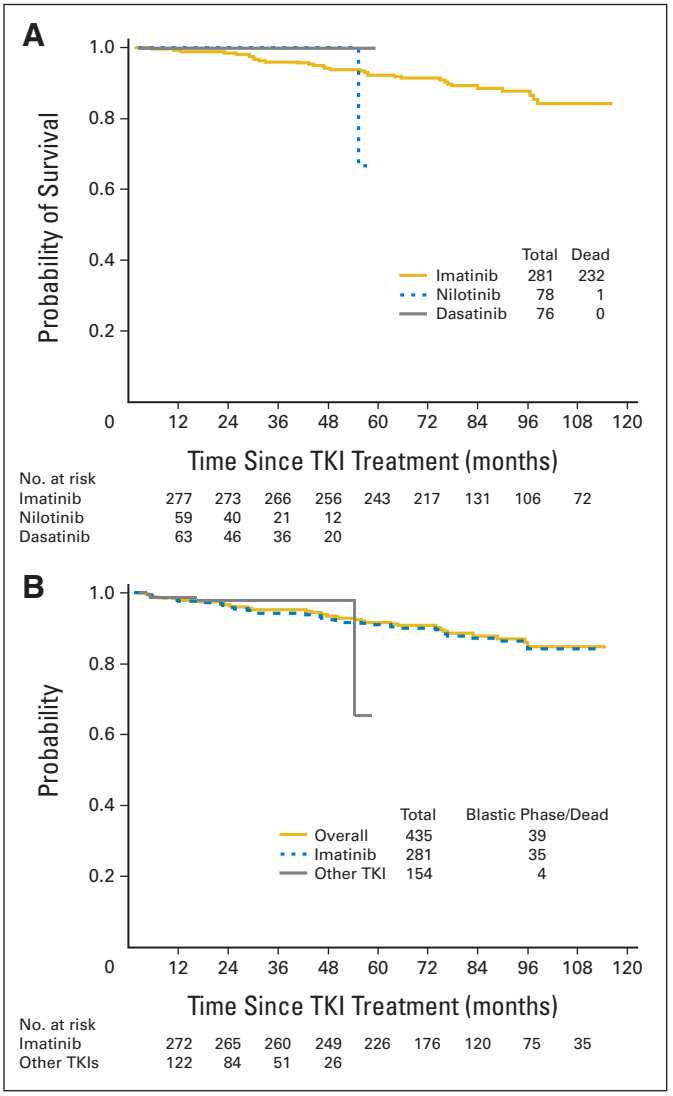

Fig 1. (A) Overall survival by treatment and (B) survival without blastic phase (events = death from any cause or blastic phase) in patients with chronic myeloid leukemia overall and by therapy. TKI, tyrosine kinase inhibitor.

RESULTS

The characteristics of the study group are listed in Table 2. Their median age was 48 years; 22% of patients were ≥ 60 years old. Forty-one percent of patients were women. The median duration of CP CML before initiation of TKI was 1 month (range, 0 to 12 months). Seven percent of patients were high risk by the Sokal risk score. The characteristics of patients treated on front-line therapies with imatinib, nilotinib, and dasatinib were similar (data not shown).[15-17]

The median follow-up time of the study group was 67 months (range, 2 to 116 months). The median follow-up was longer with imatinib (median, 84 months) compared with nilotinib (median, 24 months) and dasatinib (median, 30 months). Overall, 92% of patients achieved CCyR. The 12-month CCyR rate was 87% (83% on imatinib, 96% on nilotinib, and 97% on dasatinib). Survival by TKI therapy is shown in Figure 1A. Survival without BP overall and by TKI therapy (imatinib *v* nilotinib/dasatinib) is shown in Figure 1B.

At present, 312 (72%) of 435 patients treated remain on TKI therapy. One hundred twenty-three patients (28%) were taken off study for the following reasons: primary resistance or loss of response (n = 33), BP developing on TKI therapy (n = 6), intolerance/toxicity (n = 29), and other causes (n = 55). Among the latter 55 patients, the reasons for taking patients off TKI therapy were as follows: loss to follow-up (n = 14), noncompliance to therapy (n = 11), financial issues (n = 8), intercurrent illnesses (n = 7), patients choice (n = 5), referral to stem-cell transplantation in CP (n = 2), and death from non-CML causes (n = 8; after complications of surgery, n = 1; old age, n = 2; congestive heart failure, n = 1; pneumonia, n = 1; car accidents/suicide, n = 2; myocardial infarction, n = 1).

At present, 33 patients (7.6%) have died; eight patients died while on TKI therapy (none as a result of CML, detailed earlier), two patients died within 60 days of being taken off TKI therapy (one with acute myeloid leukemia and one with renal cancer), and 23 patients died more than 60 days after being taken off TKI therapy. In the latter 23 patients, nine deaths were associated with resistance relapse or BP (all already accounted for as events or progression while on TKI therapy); 10 patients were off treatment for toxicity or intolerance (these would

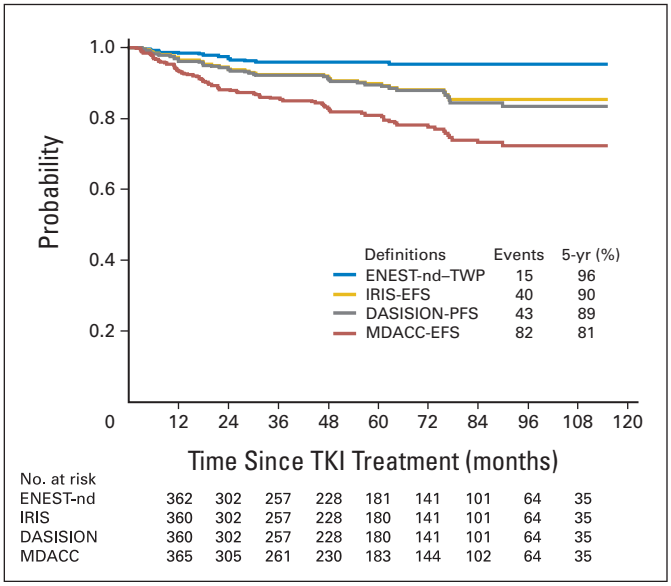

Fig 2. Outcome according to different reported definitions. DASISION, Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients; EFS, event-free survival; ENEST-nd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients; IRIS, International Randomized Study of Interferon Versus STI571; MDACC, MD Anderson Cancer Center; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TWP, time without progression; yr, year.

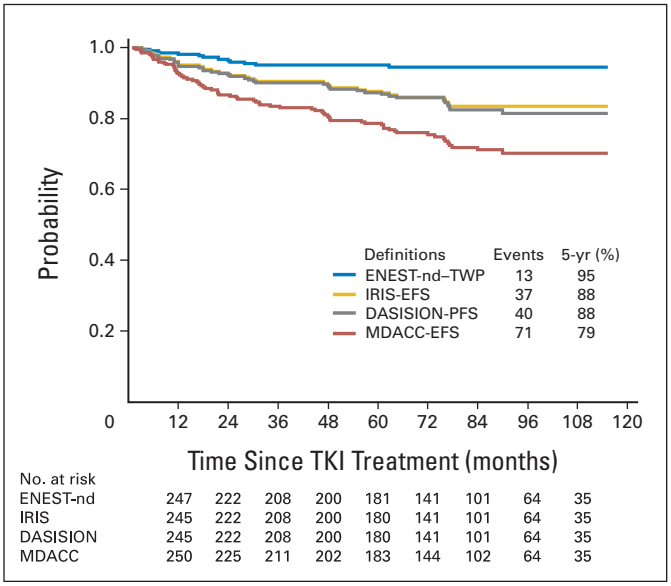

Fig 3. Outcome according to different definitions in the 281 patients treated with imatinib. DASISION, Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients; EFS, event-free survival; ENEST-nd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients; IRIS, International Randomized Study of Interferon Versus STI571; MDACC, MD Anderson Cancer Center; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TWP, time without progression; yr, year.

be censored by some definitions at the time they were taken off TKI therapy; eight of the patients later died from CML causes, one died after allogeneic stem-cell transplantation, and one died of unknown cause); and four patients were off TKI as a result of other illness, noncompliance, loss to follow-up, or patient choice (three of the patients later died from CML-related causes and one died from other causes). Thus, of the 33 deaths, only 19 (58%; eight deaths on TKI, two deaths within 60 days, and nine deaths after being off for resistant relapse or BP) would be accounted for as an event or a progression on the IRIS, ENEST-nd, or DASISION studies for PFS or EFS. The other 14 patients (42%) would be censored at the time they were taken off TKI therapy.

On the basis of the four definitions of EFS or PFS, the number of progressions/events were as follows: time without progression–ENEST-nd, 15 progressions; EFS-IRIS, 40 events; survival free from transformation to AP/BP-IRIS, 15 events (not shown in Fig 2); PFS-DASISION, 43 progression/events; and EFS-MDACC, 82 events; the corresponding 5-year PFS or EFS rates were 96%, 90%, 96%, 89%, and 81%, respectively (Fig 2). The same outcomes are shown for only the 281 patients treated with imatinib (Fig 3).

DISCUSSION

The choice of available TKIs for front-line treatment of patients with CML may depend on the long-term results as measured by PFS and EFS. Different studies have used different definitions of PFS and EFS. In some studies, patients taken off therapy for reasons other than progression or event (as variably defined) are censored at the time they are taken off study for other reasons, many of which can be reasonably considered to constitute an event. This is true for approximately 20% of patients taken off TKI therapy for toxicity on the IRIS[7,13] and other recent studies. This is justified by the limited capacity of large multi-institutional studies to observe patients taken off drug therapy beyond 30 to 60 days and also by the assumption that progression/events off the TKI treatment cannot be attributed to the inefficacy of a treatment that had already been discontinued. This approach considers that toxicity and progression/events are independent of each other, which is debatable. A patient taken off a TKI for myelosuppression or severe bone pain toxicities may transform to AP or BP within 3 to 6 months, with myelosuppression or severe bone pain being possibly early manifestations of progression. In addition, despite the widely accepted definitions of failure of therapy when patients do not achieve predetermined end points at specific times (eg, CCyR at 18 months), these measures of primary resistance are usually not counted as events in most definitions of events. Also, when analyzing PFS or EFS, some studies do not code deaths occurring beyond 30 to 60 days after treatment discontinuation if the reason for coming off study is not progression or an event (eg, toxicity). This accounts for the censoring observed in some PFS and EFS curves, even with the long-term median follow-up of patients. This censoring approach also accounts for the reported rate of survival free from transformation to AP or BP of 92% at 8 years, although the overall survival is 85% (93% if only CML-related deaths are considered). Thus, reports of survival free from transformation rates of 99% to 100% for patients who have achieved MMR at 12 months need to be considered with caution.[6]

The definition of EFS in the MDACC trials accounts for additional events that truly reflect a failure to achieve the desired goals (ie, lack of achievement of response by the European Leukemia Network criteria, being taken off therapy for toxicity, and deaths from any cause at any time after start of therapy), which may not be accounted for in large-scale randomized trials but may be accounted for in some other

trials.[18] In the latter British study, de Lavallade et al[18] reported the outcome of 204 patients with newly diagnosed CML treated with imatinib on an intent-to-treat basis, with all events recorded (presumably including stopping imatinib for toxicity as an event). By 5 years, 25% of patients had discontinued therapy for any reason (corresponds probably to an estimated 5-year EFS by this definition of 75%; similar to the 5-year EFS-MDACC of 81%), and the 5-year probability of remaining in major cytogenetic response was only 62.7%.[18] Such definitions (EFS-MDACC and study by de Lavallade et al[18]) give a more realistic picture of patients outcome because approximately 20% of patients on the IRIS trial were taken off imatinib therapy for toxicity in the first 5 years,[7] and 15% to 25% of patients have been reported to be off TKI therapy because of the study design (suboptimal response results in a change in the dose of TKI or a change to a different TKI) or because of toxicities associated with the TKIs, even with the short follow-up, on the ENEST-nd and DASISION studies.[11,12]

In this study, we compared different definitions of PFS and EFS used by different studies in CML as they relate to long-term outcome. Survival is an established outcome parameter; all deaths on study on or off TKIs should be reported. However, even for this end point, the timing of the death (eg, within 30 to 60 days from coming off study or later) may affect whether the death is captured or not. In addition, deaths may only be reported if related to CML, but in some instances, it might be difficult to determine the relationship, and some deaths might not be related to the disease, but related to TKI therapy (eg, an occasional instance of heart failure). Furthermore, the definitions of progression and event in the evaluation of PFS and EFS, respectively, are highly variable. Applying these definitions to 435 newly diagnosed patients with CML on TKI therapy, we found the measurements of PFS/EFS at 5 years to range from 81% to 96%, depending on the definition used. This substantial variation may have an impact on the interpretation of the data regarding the efficacy of new-generation TKIs when compared with each other, as well as when compared with imatinib. We have used a similar approach in defining the success of using a second-generation TKI after treatment failure with imatinib and one other TKI. Although major cytogenetic responses have been reported in 25% to 30% of patients, when accounting for the duration of response, discontinuation of therapy because of toxicity, and other events using this broader definition, the median failure-free survival time was only 20 months for patients in CP.[19] This emphasizes the need for uniform definitions of measures of long-term outcome in CML that allow a more realistic picture of the benefit of therapy and also allow a more objective comparison of data for practicing clinicians to allow them to make sound treatment decisions.

With the availability of effective salvage therapies after failure on front-line TKI therapy, many patients can receive effective salvage treatment and maintain excellent long-term outcomes. This is the case in patients with AP CML receiving TKI therapy, in whom the estimated 5-year survival exceeds 60%. This is even more relevant to other events such as cytogenetic or hematologic resistance or the development of toxicity with a particular front-line TKI. Among such patients, the estimated 3-year survival rates with second TKI salvage therapy are greater than 80%.[9,10] Thus, it can be argued that the only important events in the course of CML therapy with TKIs are ones that cannot be drastically changed (ie, BP or death from any cause). Therefore, we use a new definition to measure long-term outcome—survival without BP. The outcome of such patients by TKI therapy is shown in Figure 1B and may be used in future analyses.

In summary, this study highlights the impact of different long-term end point definitions on perceived differences in long-term outcome with TKI therapy in CML. Uniform definitions are needed to compare long-term efficacy of different CML therapies.

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