To the Editor:

The review article by Mills et al. was timely and welcome. They raised a number of points that are relevant to the study of the prognosis of chronic myeloid leukemia (CML). We would like to add three points. First, the number of patients in any series was too small to detect a difference between two groups, unless that difference was very great. Second, the assessment of chronic phase duration is not reliable, as the majority of patients progress from chronic to blastic phase (or from chronic phase to death without a true blastic phase) through an accelerated phase that is difficult to date. Survival length is much more exact and reliable than chronic phase duration. Third, the review did not or could not take into consideration the relationship between breakpoint site and other previously established prognostic features and formulations. To make a simple example, since it was established that spleen size and peripheral blood blast cell proportion are inversely related to survival length, it cannot be sufficient to report that one breakpoint site or the other is or is not related to survival length. It is necessary to know also if it is related or not, e.g., to spleen size and blast cells. If molecular lesions would correlate with prognosis and with prognostic features, this would provide the latter with a molecular basis that would be worth investigating. But this would not allow substitution of a simple and cheap prognostic factor or system with a more sophisticated and expensive one. In contrast, if molecular lesions would correlate with prognosis but not with previously established prognostic features, molecular data should be quickly incorporated into appropriate prognostic formulations.

The final message of Mills et al., calling for prospective studies in this area, was pursued by the Italian CML Study Group since 1989, and we are currently investigating the meaning of the breakpoint in an unbiased and unselected cohort of 236 Ph+CML patients who
were first seen between 1989 and 1991 and were entered into the same treatment protocol.

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REFERENCES
1. Mills KI, Benn P, Birnie GD: Does the breakpoint within the major breakpoint cluster region (M-bcr) influence the duration of the chronic phase in chronic myeloid leukemia? An analytical comparison of current literature. Blood 78:1155, 1991

RESPONSE
The points raised by Baccarani et al make an important contribution to the controversy concerning M-bcr breakpoint location and prognosis. Our review attempted to identify similarities and differences in those reports that had been published at that time to try to determine why different laboratories came to disparate conclusions. In this respect we could only compare data that had been included in those reports, although an ideal situation would have involved a comparison of all clinical and molecular data. In no way did we wish to suggest a direct substitution of breakpoint site determination for other prognostic features, but rather the addition of these data to give a more accurate prognosis.

Nevertheless, some of the studies reviewed did suggest that breakpoint location could be an important factor (although not necessarily the only one) in determining disease duration. If the molecular breakpoint is eventually shown to be a prognostic indicator, either alone or together with other features of the disease, this must suggest that it is important enough to warrant studying.

We agree that estimating chronic phase duration is not easy, but this is not so much because of difficulties in assessing the time of onset of blast crisis in the vast majority of cases because “accelerated phase” is relatively short in most patients. Much more difficult is assessing the time of onset of chronic phase, a point made in our review. Because this has the same effect on the estimate of survival time as on that of the chronic phase duration, the former is no more accurate or reliable. Indeed, it could be less so because the frequency of recurrence of blast crisis can vary enormously, depending to some extent on the therapy used in blast crisis.

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BCR-ABL breakpoint and prognosis in chronic myeloid leukemia
[letter; comment]

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