To the editor:

Clearly defined response criteria evaluating treatment of CLL patients in clinical research trials

The treatment of chronic lymphocytic leukemia (CLL) has dramatically improved over the past decade using chemotherapy regimens combined with rituximab. However, the optimal regimen has yet to be defined and clearly defined response criteria are critical for evaluating CLL patients who are treated on clinical research trials. The Guidelines from the International Workshop on CLL were first published in *Blood* in June 2008, but was replaced by an updated corrected version online on December 8, 2008.[1] These Guidelines were published to update and replace the 1996 National Cancer Institute (NCI)–sponsored Working Group Guidelines.[2] However, while this online updated manuscript is otherwise outstanding, some important issues were not clearly defined regarding response criteria in clinical research trials.

The 2 issues that require clarification include examination of the bone marrow aspirate and biopsy and computed axial tomography (CT) scans. The published version[1] redefined the 1996 bone marrow criteria guidelines for a complete response (CR) by waiting "3 months after the last treatment" to perform the marrow and requiring standard flow cytometry or immunohistochemistry negativity for a CR. It also eliminated nodular partial responses (nPRs). These criteria for CR differ from the criteria from the guideline published in 1996, which only required less than 30% lymphoma cells in the marrow for a CR.[2] The online updated version required a bone marrow examination within 2 months after the last treatment and changed the CR criteria back to the 1996 guidelines including reinstating nPR. However, it suggested that clinical trials aiming to maximize CR should assess the bone marrow for minimal residual disease (MRD) using standard flow and immunohistochemistry (1 in 10 leukocyte sensitivity) and 4-color flow or allele-specific oligonucleotide polymerase chain reaction (1 in 10 000 leukocyte sensitivity).

In the online version, Section 5.1.2, titled "Absence of significant lymphadenopathy (eg, lymph nodes $>$ 1.5 cm in diameter) by physical examination," states: "CT scans are desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter." Section 5.2.2 in the online version is titled "Reduction in lymphadenopathy (by CT scans in clinical trials or by palpation in general practice)."

It is not clear whether CT scans are mandatory for clinical trials with contradicting statements in the same online revised version. It is also not clear whether there are differences in the minimal residual disease bone marrow criteria for a CR between the published and online versions. These issues are critical for clinical trial evaluation, as CRs are highly predictive of progression-free survival and in many trials responses are the primary endpoint. It would be helpful if the authors could clarify these issues.

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Response

Defining response criteria in CLL patients treated in clinical research trials

We thank Dr Foon for his letter, which allows us to clarify a few important points.

The first question relates to the definition of (complete) response by the examination of peripheral blood counts and marrow. This point has been addressed by the final version of the manuscript[1]:

- Despite the advent of techniques for evaluation of minimal residual disease (MRD), we retained the established definition of complete response (CR)[2] to allow for comparison between the results of older trials with those completed after publication of the 2008 guidelines (see sections 5.1.1 [peripheral blood lymphocytes] and 5.1.6 [marrow]).
- In the same sections, we recommended that clinical trials aimed at maximizing the CR rate should assess for MRD by flow cytometry (described in section 5.9) or by immunohistochemistry (IHC).
- Moreover, in section 5.1.6 we recommended that lymphoid nodules found in the response-assessment marrow biopsy should be recorded as "nodular PR" and that IHC be performed to determine whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells.

The second question relates to the recommended use of computed tomography (CT) scans in clinical trials that we provided in section 5.1.2 and 5.2.2:

- We stated in section 3.5.2.2 that CT scans generally are not required for the initial evaluation or follow-up. However, we recommended that CT scans be used in clinical trials intended to maximize complete remission, one at the start of therapy and the other at first restaging after therapy if previously abnormal.
- In Table 3 of our article we point out that assessment of a PR may not require a CT scan at restaging if the residual disease can be detected by other methods (eg, blood counts or palpation).