Ibrutinib Regimens in Older Patients with Untreated CLL

TO THE EDITOR: Woyach et al. (Dec. 27 issue)¹ report that in their trial involving patients who were 65 years of age or older with previously untreated chronic lymphocytic leukemia (CLL), treatment with ibrutinib was superior to bendamustine plus rituximab with regard to progression-free survival. The authors also report that the rate of grade 5 adverse events was higher than expected with the ibrutinib-containing regimens. They thought this finding might be due to the crossover design and short follow-up. However, in the Adverse Events section of the article, the authors mention that they excluded events that occurred after crossover, so I think this finding could not have been related to the crossover design.

The rate of grade 5 adverse events, especially unexplained or unwitnessed death, appears to be significantly higher in this trial than in similar trials.^{2,3} However, the rate of grade 5 adverse events other than unexplained or unwitnessed death was consistent with that in previous reports. I think this finding might be related to lethal ventricular tachyarrhythmias that may develop in patients who receive ibrutinib.⁴

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No potential conflict of interest relevant to this letter was reported.

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4. Lampson BL, Yu L, Glynn RJ, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. *Blood* 2017;129:2581-4.

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TO THE EDITOR: Woyach et al. make a sweeping conclusion regarding the superiority of ibrutinib over bendamustine plus rituximab in older pa-

tients with CLL. Design flaws in the methods of the trial inherently lent a selection bias favoring ibrutinib by including patients with del(17p13.1) and TP53 mutations (who should not receive chemoimmunotherapy)¹ and by continuing ibrutinib until disease progression as compared with the 6 months of therapy with bendamustine plus rituximab. The lack of a between-group difference at year 1 in patients without del(17p13.1) and del(11q22.3) is testimony to this bias (Fig. S2 in the Supplementary Appendix, available with the full text of the article at NEJM.org). In addition, no improvement in outcomes was seen in patients with methylation at the promoter region of the gene encoding zeta chain-associated protein kinase 70 (ZAP70), who made up nearly half the patients (47%) (Table S2 in the Supplementary Appendix).

The significant difference between ibrutinib and bendamustine plus rituximab with respect to progression-free survival at 2 years was thus driven largely by patients with these mutations. A tempering of conclusions is warranted, since the position of ibrutinib as a first-line drug is as yet unclear and it has a great cost and potential for serious toxic effects.²

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2. Kater AP, Brown JR. Ibrutinib: searching for a partner drug. *Lancet Oncol* 2019;20:3-5.

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TO THE EDITOR: In a randomized, phase 3 trial involving patients with previously untreated CLL,

Woyach et al. found that treatment with continuous ibrutinib, either alone or combined with rituximab, was superior to six cycles of chemoimmunotherapy with regard to progression-free survival. However, the incidence of clinically significant nonhematologic adverse events was higher among the patients who received ibrutinib-containing regimens.

Inhibition of Bruton's tyrosine kinase (BTK) by ibrutinib has emerged as a crucial strategy for treating B-cell cancers. However, BTK also plays a major role in the development and functioning of adaptive immunity, including fungal immune surveillance. Recent studies have shown higher-than-expected rates of life-threatening invasive fungal diseases among patients who have received ibrutinib. These diseases usually occur early in the course of treatment and manifest with nonclassic features.^{1,2} Table S7 in the Supplementary Appendix of the article by Woyach et al. shows a 19.1% rate of infection of grade 3 or higher (in 69 of 361 patients) among patients who received ibrutinib in the trial.

Could the authors provide additional information on the underlying species and clinical manifestations of these infections, especially with respect to fungal pathogens? Given the alarming incidence of invasive fungal diseases in some studies,³ we think that this aspect should be properly addressed in current and ongoing prospective multicenter trials.⁴

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Dr. Janssens reports receiving consulting fees, speaker's fees, and travel support from Janssen Pharmaceutica. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: In reply to Diker: in our article, we meant that the similar overall survival among patients in the three groups may be due to the crossover design and relatively short follow-up for the overall survival end point. However, we do agree with the comment that the unexplained or unwitnessed deaths could have been related to the lethal ventricular arrhythmias that have been seen with ibrutinib treatment, and this is noted in the Discussion section of our article. This association has been reported by multiple groups, and the mechanism of arrhythmias and identification of at-risk patients are the subjects of active investigation.

We do not agree with Sengar et al. that there were methodologic flaws in our trial. The inclusion of patients with del(17p) or TP53 mutations was intentional, since the crossover design of the trial allowed all patients to receive ibrutinib at a time when this drug was not available outside a clinical trial. Figure 2B, and Figure S2C in the Supplementary Appendix, show that among patients without del(17p) or del(11q), ibrutinib-containing regimens were superior to bendamustine plus rituximab with regard to progression-free survival. Sengar and colleagues are correct that at this time there does not appear to be a difference in progression-free survival among the treatment groups in patients with ZAP70-methylated disease. However, the trial was not powered to detect differences within subgroups, so trends should be interpreted with caution. In addition, most patients with ZAP70-methylated disease remained in remission, so longer follow-up is needed before firm conclusions can be made for this group. The superiority of ibrutinib over bendamustine plus rituximab in terms of progression-free survival in the entire patient population is clear, and this trial, along with others,^{1,2} has shown that ibrutinib is more effective than chemotherapy or chemoimmunotherapy.

Mercier et al. raise an important point about the risk of invasive fungal infections with ibrutinib. In this trial, toxic effects were documented and graded according to the Common Terminology Criteria for Adverse Events, and the investigators could provide additional comments regarding these toxic effects. Therefore, we knew of specific infection types only if this information was volunteered by investigators at the sites. One patient was noted to have aspergillus pneu-

monia, but no other cases of invasive fungal infections were reported. An analysis of adverse events in this trial, with data on the types and sites of infections, including fungal infections, is under way.

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