the generalizability of our results because of the exclusion of patients who received previous neuromuscular blockade. In a prespecified analysis, we determined that there was no interaction between treatment effect and a site's incidence of exclusion for previous use of neuromuscular blockade (Table S11 in the Supplementary Appendix, available with the full text of our article at NEJM .org). Even at the many sites where patients were rarely excluded for previous use of neuromuscular blockade, there was no evidence of benefit with a continuous infusion of neuromuscular blockade.

Gallo de Moraes et al. comment that some patients with ARDS may still benefit from early neuromuscular blockade, including those with severe refractory hypoxemia or ventilator dyssynchrony. As in the ACURASYS trial, we provided recommendations for the use of neuromuscular blockade in the control group, and 17.1% of these patients did receive boluses (as opposed to 22.2% in the ACURASYS trial) during the 48-hour intervention period.[1] Therefore, we did not conclude that neuromuscular blockade should never be used in patients with moderate-to-severe ARDS, only that there was no advantage to the systematic use of early continuous infusions.

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Since publication of their article, the authors report no further potential conflict of interest.

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Ibrutinib and Venetoclax for First-Line Treatment of CLL

TO THE EDITOR: In their phase 2 study, Jain et al. (May 30 issue)[1] investigated the efficacy of ibrutinib and venetoclax in previously untreated patients with chronic lymphocytic leukemia (CLL). Currently, it is unknown whether this combination is efficacious in patients with relapsed or refractory CLL.

In the VISION/HOVON141 trial (ClinicalTrials .gov number, NCT03226301), we assessed the efficacy and safety of ibrutinib and venetoclax in patients with relapsed or refractory CLL. A preplanned interim analysis was performed after six cycles of full-dose ibrutinib and venetoclax in 51 patients. The overall response rate (according to International Workshop on Chronic Lymphocytic Leukemia [IWCLL] criteria) was 96% (clinical complete remission or complete remission with incomplete count recovery, 67%, and partial response, 29%; the rates were 73% and 27%, respectively, among patients with previously untreated CLL). On eight-color flow cytometry (sensitivity, $<10^{-4}$), the rate of undetectable minimal residual disease in blood was 29% among patients who received ibrutinib and venetoclax (40% in bone marrow among patients with previously untreated CLL). The rate of undetectable minimal residual disease increased over time to 47% in blood (52% in bone marrow among patients with previously untreated CLL) after nine cycles of full-dose ibrutinib and venetoclax among 41 patients.

A high concordance between levels of minimal residual disease in blood and bone marrow with regimens containing venetoclax has been reported.[2] Despite caveats regarding comparisons across trials, preliminary data in the VISION/HOVON141 trial indicate that the high efficacy of the combination of ibrutinib and venetoclax was also maintained in patients with relapsed or refractory CLL.

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THE AUTHORS REPLY: Kater and colleagues report the efficacy of the combination of ibrutinib and venetoclax in 51 patients with relapsed or refractory CLL. They report that 67% of the patients who received this combination therapy for 6 months had a clinical complete remission or complete remission with incomplete count recovery, and the rate of undetectable minimal residual disease in blood was 29%. These results indicate the effectiveness of this combination regimen in relapsed or refractory CLL.

The results of two additional studies evaluating combined ibrutinib and venetoclax in patients with relapsed or refractory CLL have been reported. In the CLARITY trial reported by Hillmen and colleagues, 54 patients with relapsed or refractory CLL received ibrutinib and venetoclax.[1] They reported a rate of complete remission or complete remission with incomplete count recovery of 51% (according to IWCLL criteria) after 12 months of treatment with the combination therapy; the rates of undetectable minimal residual disease in blood and bone marrow were 53% and 36%, respectively. As mentioned in our article, 80 patients with relapsed or refractory CLL received treatment in our trial; the preliminary results in this cohort were presented at the American Society of Hematology meeting in 2017.[2]

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Since publication of their article, the authors report no further potential conflict of interest.

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