THE AUTHORS REPLY: Eskazan speculates that a regimen using daunorubicin at a dose of 90 mg per square meter (with or without midostaurin) would lead to superior outcomes as compared with the regimen of daunorubicin at a dose of 60 mg per square meter plus midostaurin that was used in the CALGB 10603 trial. However, at the time that the trial was designed, neither the results showing the superiority of induction with daunorubicin at a dose of 90 mg per square meter as compared with 45 mg per square meter in *FLT3*-mutated AML[1] nor those suggesting that the higher dose of this anthracycline might be better than 60 mg per square meter in *FLT3*-mutated AML[2] were available. These cited data are derived from retrospective analyses that were not powered to show significant differences. With all the caveats involved in comparing one trial with another, the results with the induction of daunorubicin at a dose of 60 mg per square meter plus midostaurin in the CALGB 10603 trial were, if anything, slightly better than the results with a dose of 90 mg per square meter in the Eastern Cooperative Oncology Group 1900 (E1900) trial[1] and the U.K. Medical Research Council AML17 trial.[2]

A detailed analysis of the effect of *NPM1* comutations on the outcome in each group of the CALGB 10603 trial is of interest. In the preliminary trial, concurrent administration of midostaurin and chemotherapy had neither a better side-effect profile nor better efficacy[3] than the sequential schedule used in the CALGB 10603 trial. However, we agree that further exploration of midostaurin schedules and effects on target inhibition are warranted.

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1. Luskin MR, Lee J-W, Fernandez HF, et al. Benefit of high-dose daunorubicin in AML induction extends across cytogenetic and molecular groups. Blood 2016;127:1551-8.
2. Burnett AK, Russell NH, Hills RK. Higher daunorubicin exposure benefits FLT3 mutated acute myeloid leukemia. Blood 2016;128:449-52.
3. Stone RM, Fischer T, Paquette R, et al. Phase IB study of the FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. Leukemia 2012;26:2061-8.

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Acute Respiratory Distress Syndrome

TO THE EDITOR: In their review of the acute respiratory distress syndrome (ARDS) (Aug. 10 issue),[1] Thompson et al. recommend that patients be placed in the prone position when the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:FIO_2) is less than 120 mm Hg. However, the guidelines for the mechanical ventilation of patients with ARDS[2] recommend this strategy for patients with severe ARDS, which the guidelines define as a Pao_2:FIO_2 of less than 100 mm Hg. Furthermore, one of the inclusion criteria for a trial that showed a decrease in mortality with this maneuver was a Pao_2:FIO_2 of 150 mm Hg or less.[3] In regard to neuromuscular blocking agents, Thompson et al. recommend the use of such drugs when the Pao_2:FIO_2 is less than 150 mm Hg. This statement is in agreement with the guidelines for the use of neuromuscular blocking agents in critically ill patients,[4] but the trial conducted by Papazian et al., which is cited by the authors, showed that these agents had a beneficial effect on survival at 90 days for patients with a baseline Pao_2:FIO_2 of less than 120 mm Hg.[5] This finding has important clinical relevance, since the thresholds defined for the initiation of interventions, if unclear, may lead to inappropriate exposure to these interventions or delays in their withdrawal, either of which may put patients at risk.

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

1. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562-72.
2. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253-63.
3. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
4. Murray MJ, DeBlock H, Erstad B, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 2016;44:2079-103.
5. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.

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TO THE EDITOR: Thompson et al. do not include drugs as a possible trigger for ARDS. For example, some of the drugs used to treat cancer, such as cytarabine, gefitinib, gemcitabine, vinblastine, and vincristine, are a well-recognized cause of ARDS.[1,2] Amiodarone, infliximab, nitrofurantoin, verapamil, narcotics, and overdoses of salicylates have also been implicated as causes of ARDS. Overall, drugs are implicated in approximately 13% of patients with ARDS in the absence of other identified precipitating factors.[3] Although for most drugs the exact mechanism of pulmonary toxicity has not been elucidated, direct, drug-induced damage of pulmonary vascular endothelial cells and alveolar epithelial cells has been suggested.[2] Drug-induced ARDS should be considered if the cause of lung injury is not evident.[4] The diagnosis of drug-induced ARDS is based on a history of drug exposure, with a temporal relation between the introduction of the drug and the onset of symptoms, and on the exclusion of other causes of acute lung injury. Treatment is based on timely withdrawal of the offending drug and the provision of supportive measures.

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

1. Ben-Noun L. Drug-induced respiratory disorders: incidence, prevention and management. Drug Saf 2000;23:143-64.
2. Lee-Chiong T Jr, Matthay RA. Drug-induced pulmonary edema and acute respiratory distress syndrome. Clin Chest Med 2004;25:95-104.
3. Gibelin A, Parrot A, Maitre B, et al. Acute respiratory distress syndrome mimickers lacking common risk factors of the Berlin definition. Intensive Care Med 2016;42:164-72.
4. Ben Salem C, Hmouda H, Bouraoui K. Acute lung injury and acute respiratory distress syndrome. Lancet 2007;370:383-5.

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THE AUTHORS REPLY: The official clinical practice guideline of the American Thoracic Society, the European Society of Intensive Care Medicine, and the Society of Critical Care Medicine strongly recommends the use of the prone position in patients with a Pao_2:Fio_2 of 100 mm Hg or less; this approach is supported by data showing a lower risk of death, as compared with the use of mechanical ventilation in the supine position. However, there was a lack of consensus regarding the use of the prone position in patients with a Pao_2:Fio_2 of 101 to 150 mm Hg owing to a "lower confidence in the balance between desirable as compared with undesirable outcomes in this subgroup of patients."[1]

As we noted in our review, a recent global survey of more than 29,000 patients who received mechanical ventilation showed that ARDS, even in its severest form, is underrecognized.[2] The prone position was used in only 16.3% of patients recognized by clinicians as having severe ARDS (patients with a Pao_2:Fio_2 of less than 100 mm Hg), the subset in which the evidence of benefit is strongest and for which we have consensus. Accordingly, increased recognition of ARDS and increased use of ventilation with patients in the prone position in the subset of patients with severe disease should be high priorities.[1,2] We agree with Jaramillo-Rocha that thresholds should also guide the decision to change from the prone to the supine position at a Pao_2:Fio_2 of at least 150 mm Hg, measured approximately 4 hours after returning to ventilation in the supine position, with a positive end-expiratory pressure of 10 cm of water or less and an Fio_2 of 0.6 or less, as reported by Guérin et al.[3]

We agree that drug-induced lung disease should be considered when assessing a patient with ARDS and note this in Table 3 of our article, available at NEJM.org. We thank Ben Salem for drawing attention to this important clinical caveat.

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

1. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253-63.
2. Bellani G, Laffey JG, Pham T, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. Am J Respir Crit Care Med 2017;195:67-77.
3. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.

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The congress will be held in Berlin, June 20–23. Deadline for submission of abstracts and papers is Jan. 10.

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