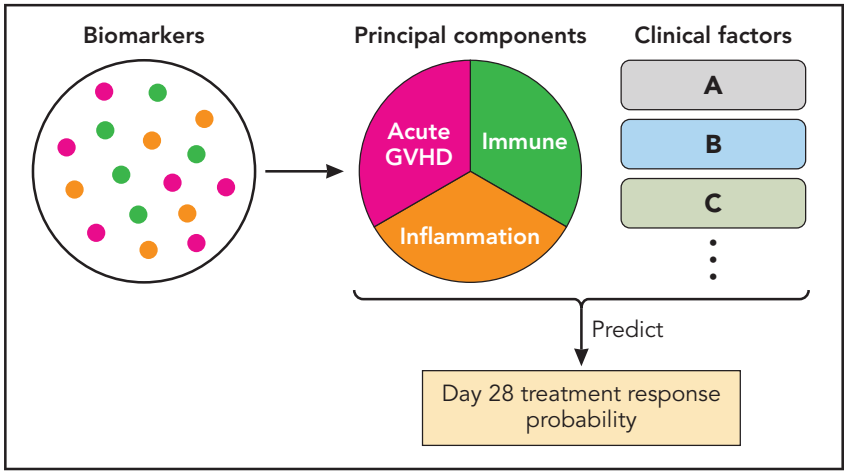

The analytic method used by Socié et al. The biomarkers were grouped into 3 major categories of principal components and then analyzed with clinical factors. GVHD, graft-versus-host disease. Professional illustration by Patrick Lane, ScEYEnce Studios.

treatment for acute GVHD.[5] A notable point is that both proteins showed reasonably large differences between responders and nonresponders in this study. Also interesting is that the B cell marker and IL-6 showed the largest differences between the groups, although B cells are thought to be conventionally more important in chronic GVHD than in acute GVHD. The biological implications of these observations need further study. As acknowledged by the authors, the biomarker panel could be optimized further, without losing much precision, by selecting biomarkers with large principal component coefficients. Panels with fewer biomarkers would be more realistic for routine clinical use.

What were the most relevant biomarkers for predicting treatment response specifically to ruxolitinib? The authors explored interaction analyses and found no differential response in biomarker subgroups between the treatment arms. Thus, the current models predict treatment response regardless of treatment type, and further studies are warranted to identify biomarkers that predict treatment response specifically to ruxolitinib. An important goal now is to define ruxolitinib-refractory or -dependent patients with GVHD. A new working definition was proposed recently, with at least 14 days of treatment recommended to define lack of improvement.[6]

How will the models reported here inform practice? An important point to recognize is that this approach is a probability engine that tells us probabilities of response, rather than a classification engine that tells us positive and negative predictive values in predicting response. By using the probability engine, we will know an expected probability of response in an individual patient with steroid-refractory or steroid-dependent acute GVHD. Such information may help inform our clinical decision when we need to start second-line systemic treatment. Furthermore, if we can predict the probability of subsequent response based on clinical and biomarker information at day 14 or even earlier, this prediction may help us in initiating third-line treatment earlier. Future studies should clarify reliable cutoff probabilities for treatment choice or change. Verification is needed in independent cohorts to prove the applicability and utility of the current models for use in clinical trials and in practice.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Santoro et al, page 2780

Targeted therapy in mediastinal gray zone lymphoma

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In this issue of *Blood*, Santoro and colleagues report results from the CHECKMATE436 clinical trial that prospectively enrolled a cohort of 10 patients with mediastinal gray zone lymphoma (MGZL), a rare subtype of aggressive non-Hodgkin lymphoma.[1] The combination of the anti-CD30 antibody brentuximab vedotin (BV) with the anti-programmed cell death protein 1 (PD1) antibody nivolumab (nivo) demonstrated significant antitumor activity in this challenging lymphoma subtype.

The BV-nivo combination is rational based on our knowledge of the pathobiology of MGZL. CD30 antigen expression and upregulation of the PD1 pathway are the

hallmarks of this lymphoma subtype.[2,3] The single-agent activity of brentuximab has not been well studied in MGZL, but some studies with small numbers of patients with MGZL have included it combined with other agents.[4] There are also a few case reports of responses in small numbers of patients with MGZL treated with nivo or pembrolizumab.[5,6]

Given the small number of published MGZL cases treated with novel therapies, the investigators on this study are to be congratulated for accruing 10 patients with this rare form of lymphoma. The data showed impressive activity of the BV-nivo combination in relapsed or refractory MGZL with an overall response rate of 70% and 5 of 10 patients achieving complete response. Half of the patients were able to proceed to a consolidative autologous (1) or allogeneic (4) stem cell transplant (SCT). The median progression-free survival was 21.9 months, and the median overall survival was not reached. No new safety signals were identified. These data are in line with the published experience with BV-nivo in relapsed or refractory classical Hodgkin lymphoma (cHL) and primary mediastinal large B-cell lymphoma (PMBL), in which excellent activity with a favorable safety profile has been reported.[7,8]

The treatment algorithm for MGZL has been largely based on aggressive B-cell lymphomas.[9] Anthracycline-based chemotherapy and salvage chemotherapy and autologous SCT have been considered the standards of care, with a few prospective studies and retrospective series reporting inferior outcomes when compared with diffuse large B-cell lymphoma.[10] Experience with chimeric antigen receptor T-cell (CART) therapy remains very limited. Therefore, the data from CHECKMATE-436 with BV-nivo highlight the efficacy of novel therapy in the setting of relapsed or refractory disease and the potential to bridge patients toward curative SCT.

Although the management of lymphoma has generally been defined by the results of well-conducted randomized controlled trials, it is not feasible to perform these types of studies in rare lymphoma subtypes. For these indications, prospective single-arm data and even case series are important sources of data to help guide clinical decision-making. Given the accumulated evidence of the safety of this regimen in multiple disease settings as well as the similarity of efficacy reported in 3 related lymphoma subtypes (cHL, PMBL, MGZL), these data suggest that this is a valid option for patients with relapsed or refractory disease. BV-nivo may be reasonable therapy for patients who require a palliative regimen or a regimen that can be used as a bridge to SCT and/or CART therapy.

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