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Ivosidenib and Azacitidine in IDH1-Mutated AML.

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followed by natural infection (airway mucosal route) as compared with intramuscular vaccination (systemic route). There is now evidence that critical components of the mucosal immunity network play a key role in fighting SARS-CoV-2 infection,[2-5] including secretory immunoglobulin A and tissue-resident memory cells (elements of local adaptive immunity) and mucosa-associated invariant T cells, mucosal complement activation, and mucosal interferons (elements of local innate immunity).

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THE AUTHORS AND A COLLEAGUE REPLY: We agree with Matuchansky that mucosal immunity is an important area for further study, particularly in investigating the differences between infection-acquired and vaccine-acquired protection against SARS-CoV-2 infection. We are examining this in a nested cohort of participants in the SIREN study who are coenrolled in the PITCH (Protective Immunity from T Cells in Healthcare Workers) Study,[1] which investigates cellular immune responses and mucosal immunity.

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Dr. Klenerman reports no potential conflict of interest relevant to this letter. Since publication of their article, the authors report no further potential conflict of interest.

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Ivosidenib and Azacitidine in *IDH1*-Mutated AML

TO THE EDITOR: In the AGILE trial, Montesinos et al. (April 21 issue)[1] found a significant overall survival benefit of ivosidenib–azacitidine over azacitidine monotherapy in patients with *IDH1*-mutated acute myeloid leukemia (AML) who were ineligible for induction chemotherapy. Clinical decision making in this scenario requires a comparison between ivosidenib–azacitidine and venetoclax-based schemes.

Adjusted indirect comparisons that involve pooled populations are methodologically objectionable. Subgroup analyses have an increased probability of alpha and beta errors.[2] Thus, we conducted adjusted indirect comparisons (Bucher's method[3]) with pooled data[4] and subgroup trial results[5] for venetoclax–azacitidine as compared with ivosidenib–azacitidine in patients with previously untreated *IDH1*-mutated AML. We found no significant differences between treatments in adjusted indirect comparisons of overall survival, either in pooled data (hazard ratio for death, 0.43; 95% confidence interval [CI], 0.16 to 1.16) or subgroup trial results (hazard ratio, 0.64; 95% CI, 0.24 to 1.70). The small number of patients who received venetoclax–azacitidine, broad confidence intervals, and low statistical power are limitations.

The use of imprecise adjusted indirect comparisons in clinical decision making should be undertaken with caution. Interesting results obtained with venetoclax–azacitidine should not be completely rejected, but they are less reliable than data on ivosidenib–azacitidine. It seems reasonable to provisionally prefer ivosidenib–azacitidine

until a confirmatory trial of venetoclax–azacitidine involving patients with untreated AML with *IDH1* mutations has been conducted.

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

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TO THE EDITOR: We wish to highlight troublesome characteristics of the AGILE trial. First, the control treatment of azacitidine is inferior to venetoclax plus azacitidine in patients with AML who are ineligible for intensive induction.[1] Trial recruitment (including U.S. centers) continued through May 2021, after the inferiority of azacitidine to azacitidine plus venetoclax had been shown. We are unaware of any data suggesting that ivosidenib plus azacitidine would be superior to venetoclax plus azacitidine. Unfortunately, substandard control groups are frequent in industry-sponsored randomized trials.[2]

Second, ivosidenib was approved by the Food and Drug Administration in 2018[3] and is used as a salvage therapy when progression occurs. However, only two patients in the control group received ivosidenib at progression, and only 21.6% received any subsequent targeted therapy for AML. This lack of adequate postprotocol therapy (that has previously proved to be effective) is also common among contemporary randomized trials in oncology.[4]

Third, the trial switched end points and was halted early — tactics that can exaggerate the effect size.[5] Given these limitations, we do not believe this trial to be a practice-changing trial.

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Dr. Goodman reports receiving consulting fees from Seattle Genetics (now Seagen) and EUSA Pharma. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: The adjusted indirect comparison between the ivosidenib–azacitidine and venetoclax–azacitidine regimens with the use of Bucher's method has several caveats, including the incorrect assumption that the trials (AGILE and VIALE-A[1]) are similar with respect to trial population and design. Unlike the AGILE trial, the ad hoc analyses of the subgroup with *IDH1*-mutated AML in the VIALE-A trial and the pooled analysis[2] are not based on a randomized design. In the VIALE-A trial, only 11 patients with *IDH1*-mutated AML were assigned to the placebo–azacitidine group, which makes the estimates of median overall survival and the hazard ratios highly unreliable. Therefore, the results from this adjusted indirect comparison should be interpreted with skepticism.

In response to Goodman et al., we object to the statement that the control group of the

AGILE trial was substandard. In the United States, venetoclax–azacitidine became an approved treatment option for patients who are ineligible for intensive chemotherapy in November 2018. Two patients from the United States were enrolled before this date, and enrollment in the United States was stopped in October 2018. The AGILE trial was a global trial that enrolled patients almost exclusively in Europe, Asia, and Brazil, where venetoclax–azacitidine had not been approved and was not an available treatment option. Regarding salvage therapy within the AGILE trial, ivosidenib could not be considered a post-protocol salvage therapy because the agent has also not been approved by the European Medicines Agency. Other salvage therapies were used on the basis of the investigators' judgment. The percentage of patients receiving subsequent therapy for AML was similar in the two treatment groups. Changing the primary end point from overall survival to event-free survival allowed for direct assessment of the activity of protocol therapy while adjusting the sample size to a feasible range, given the rarity of *IDH1*-mutated AML and in consideration of the emerging treatment landscape. The results for overall survival and all other key secondary end points of clinical response were robustly positive. The change in the primary end point was discussed with regulatory agencies. The decision by the sponsor to discontinue further recruitment followed the recommendation of the independent data monitoring committee. To account for the unplanned interim analysis by the data monitoring committee, an individual set of group-sequential boundaries was applied to the primary and key secondary end points, which maintained the stringency for statistical significance.

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

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Rilzabrutinib in Immune Thrombocytopenia

TO THE EDITOR: In their article on a phase 1–2 trial, Kuter et al. (April 14 issue)[1] report promising results with the use of rilzabrutinib, an oral, reversible covalent inhibitor of Bruton's tyrosine kinase, in previously treated patients with immune thrombocytopenia. Although patients with infection with hepatitis B or C virus or the human immunodeficiency virus were excluded from the study, *Helicobacter pylori* infection was not mentioned in the protocol. *H. pylori* infection is linked to secondary immune thrombocytopenia, and several studies have shown improvements in the platelet count after *H. pylori*–eradication therapy in patients with immune thrombocytopenia.[2,3] Patients should be carefully assessed for *H. pylori* infection, especially in countries where this infection is prevalent, such as Japan, Italy,[2,4] the Czech Republic, and Bulgaria, the latter two being the countries where the trial was conducted.

Similarly, other types of secondary immune thrombocytopenia complicated by the presence of an autoimmune disease require cautious evaluation because the pathologic mechanisms involved are different from those in primary immune thrombocytopenia.[4,5] However, it is noteworthy that a patient death in the trial conducted by Kuter et al. that occurred after exacerbation of Evans syndrome was considered by the investigators to be unrelated to rilzabrutinib.[1]

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