To the editor:

Toxicity of laromustine plus high-dose cytarabine in patients with relapsed acute myeloid leukemia

We are writing to clarify the interpretation of results contained within a paper by Giles et al.1 In their abstract, the authors state, “The [complete remission] CR rate was significantly higher for the laromustine/[high-dose cytarabine] HDAC group (35% vs 19%, \( P < .005 \)). However, the 30-day mortality rate and median progression-free survival were significantly worse in this group compared with HDAC/placebo (11% vs 2%, \( P = .016 \); 54 days vs 34, \( P = .002 \)). [Overall survival] OS and median response durations were similar in both groups.”

The conclusion of Giles et al that “OS and median response duration were similar in both groups” understates the detrimental effect observed in the interim analysis of OS when laromustine was added to HDAC. The estimated median OS reported for the placebo/HDAC arm compared with the laromustine-plus-HDAC arm was 176 and 128 days, respectively (log rank \( P = .087 \)). Failure to reject the null hypothesis in the statistical tests used by Giles et al at the \( \alpha = .05 \) level does not imply that the OS was similar in both groups.

Giles et al presented data in their Table 4 summarizing the causes of deaths due to adverse events within 30 days from day 1 of HDAC.1 In the trial, laromustine could be administered in up to 2 induction treatments and as consolidation therapy. These possible multiple laromustine administrations extend considerably beyond the 30-day observation period from the start of HDAC. Hence, reviewing the causes of death due to adverse events throughout the trial is more appropriate than selecting the limited time period of 30 days from day 1 of HDAC.

Accompanying our letter is a table, provided by FDA and numerically identical to that presented at a meeting of the Oncologic Drugs Advisory Committee on September 1, 2009 (Table 1) highlighting the 2 most frequent causes of death due to adverse events during the study.

We further note that the 15 pulmonary deaths observed on the laromustine-plus-HDAC arm represented 21% of the deaths on this treatment, whereas no pulmonary deaths were observed on the placebo-plus-HDAC arm. Pulmonary toxicities leading to death included hypoxia, acute respiratory distress syndrome, pneumonitis, respiratory failure, respiratory distress, and pulmonary alveolar hemorrhage. The category of infectious deaths included pneumonia.

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References

Table 1. Grade 5 adverse events

<table>
<thead>
<tr>
<th>Adverse events with death</th>
<th>Placebo + HDAC (N = 86)</th>
<th>Laromustine + HDAC (N = 177)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Infectious deaths</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Pulmonary deaths</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

N indicates number of patients; and n, number of deaths.
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