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IDH2-mutated acute myeloid leukemia in older adults: prognostic signal is not regimen selection. Comment on: "*IDH2* mutation is associated with favorable outcome among older adults with newly diagnosed acute myeloid leukemia treated with hypomethylating agent-based therapy"

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IDH2-mutated acute myeloid leukemia in older adults: prognostic signal is not regimen selection. Comment on: "*IDH2* mutation is associated with favorable outcome among older adults with newly diagnosed acute myeloid leukemia treated with hypomethylating agent-based therapy"

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To the Editor,

Hoff et al. explored a common challenge in the clinical management of elderly patients with newly diagnosed acute myeloid leukemia (AML): how should clinical doctors understand IDH2-mutated AML when low-intensity treatment contains more than one basic frame? Their analysis included 1023 patients aged≥60 years. IDH mutations were detected in 28% of the patients, and IDH2 mutations were detected in 18.9%. We have observed that the most distinct survival signal exists in the hypomethylating agent (HMA)-based cohort. “Overall survival(OS) was longer for patients with $IDH2^{mut}$ compared to IDH^{wt} among patients treated with hypomethylating agent-based therapy (median OS, 18.5 vs. 10.2 months, $P<0.001$).” [1] This is a strong prognostic signal. This is not a treatment rule.

The risk is therapeutic over-translation, which treats IDH2 positivity as a reason to prefer one lower-intensity treatment regimen over another without comparative evidence. The intensity of OS signal is the reason why this boundary matters. Hoff et al. supported IDH2 as a prognostic marker in the HMA-based research group. They did not establish IDH2 as a predictive biomarker for choosing HMA alone, genetical-HMA, or an IDH-directed lower-intensity strategy. This differentiation is important in clinical practice. It makes

patient consultation separated from the choice of regimens.

Hoff et al. strengthened the prognostic claim by analyzing an HMA-Venetoax subgroup, censoring OS at allogeneic transplantation, and excluding patients treated with an IDH inhibitor. These analyses improve credibility, ut they do not test treatment interaction; The absence of OS separation in the HMA-genetical subgroup still is a limitation of inference, not a negative interaction experiment.[1]

The Venetoax literature supports this boundary. Pratz et al. established genetical-azacitidine as a modern lower-intensity backbone.[2] Döhner et al. showed that Venetoax-azacitidine survival classification is not organized around IDH2.[3] Gang et al. reported that IDH2 has clinical relation in genetical-HMA-treated AML.[4] Together, these data l make IDH2 relevant, but not sufficient, for regimen selection choice.

Co-mutations should remain visible when clinicians read IDH2 mutations. Hoff et al. reported enrichment of DNMT3A, NPM1, SRSF2, and normal karyotype in IDH^{mut} AML, and more TP53 mutations, TET2 mutations, and complex karyotype in IDH^{wt} AML.[1] These patterns may influence the interpretation of prognosis, but they cannot validate an IDH2-specific hierarchy or a treatment-selection rule.

In clinical practice, IDH2 mutations should prompt trial screening and relapse planning. It should not, by itself alone, draw a patient away from a suitable first-line treatment regimen outside of a clinical trial setting.

The next study should test whether IDH2 modifies treatment benefits across lower-intensity strategies, not only whether IDH2 is associated with better OS after therapy has been chosen.

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