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Response to Comment on: "Treatment of therapy-related acute myeloid leukemia and acute myeloid leukemia with myelodysplasia-related changes: a comparative analysis of higher-dose intensive 7+3 induction chemotherapy *versus* liposomal cytarabine and daunorubicin"

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To the editor

We thank Dr. AlJohani for his thoughtful comments[1] on our comparative analysis of higher-intensity double-induction 7+3 versus liposomal cytarabine and daunorubicin (CPX-351) in patients aged 60-75 years with therapy-related AML (t-AML) and AML with myelodysplasia-related changes (AML-MRC).[2] The overall survival (OS) advantage observed with CPX-351 for patients who achieved complete remission (CR) or CR with incomplete hematologic recovery (CRi) and proceeded to allogeneic hematopoietic cell transplantation (allo-HCT) is a clinically important observation in a population for whom allo-HCT remains the only curative option.

However, this subgroup is highly selected as these patients obtained a CR/CRi with CPX-351, remained eligible for allo-HCT, and were successfully transplanted. Evaluating the two induction strategies requires considering the full treatment trajectory, beginning with the probability of reaching CR/CRi. In this difficult-to-treat population, that probability differs substantially between treatment groups: 32% (58/180) of the higher-intensity 7+3 cohort failed to achieve CR/CRi compared with 52% (80/153) in the CPX-351 cohort. Importantly, even a substantial difference in CR/CRi rates does not necessarily translate into a difference in OS, as long-term outcomes depend on subsequent consolidation with allo-HCT. In older t-AML/AML-MRC patients, however, failure to achieve CR/CRi often precludes proceeding to allo-HCT, making the achievement of CR/CRi a prerequisite for any potential benefit of a deeper remission. Consequently, when assessed from diagnosis rather than from the selected subset of patients who achieved CR/CRi, a larger proportion of patients ultimately underwent allo-HCT in CR/CRi after higher-intensity 7+3 (66/180, 37%) than after CPX-351 (41/153, 27%).

The depth of remission achieved before allo-HCT is a key determinant of post-transplant outcomes[3,4], and morphologic CR/CRi does not fully capture measurable residual disease (MRD) status. The absence of systematic MRD assessment is a limitation shared by both cohorts[2,5] and we could not determine whether the type of intensive induction therapy affects the quality of remission and the subsequent risk of post-allo-HCT relapse. Indeed, the ongoing randomized clinical trial (NCT03897127), with post-induction MRD status and post-allo-HCT outcomes stratified by induction arm, will hopefully answer this open question. That trial will in fact address two distinct questions, namely which regimen brings more patients to a curative transplant, and which regimen produces the deepest remission once a patient reaches CR/CRi. Remission frequency and remission quality are both important treatment goals, and an ideal induction strategy should maximize both.

We are grateful for Dr. AlJohani's engagement with our analysis, and we agree that MRD data will be essential to determine whether CPX-351 yields higher-quality remissions. Until such data are available, we believe that maximizing the proportion of patients who achieve CR/CRi remains a critical consideration.

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