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Response to Comment on: "Reporting blast percentage for response assessment in acute leukemias: recommendations from an EHA/ELN expert panel"

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To The Editor:

We thank Drs Przepiorka and Jen for their thoughtful perspective(1) on the recently published EHA / ELN guidelines for reporting blast percentage in acute leukemia(2) and welcome the opportunity to clarify several key aspects of our recommendations and address their comments.

Integrating results from different test platforms is *a sine qua non* of accurate diagnostics in acute leukemia, reflecting the evolution of the field beyond sole reliance on morphology at diagnosis and response assessment. Up to now there has been no standardized framework to guide this integration at response evaluation in acute leukemias. This has led to variability among clinicians and data managers in determining which diagnostic platform is most accurate and appropriate for reporting blast response across different acute leukemia subtypes. Our guidelines aim to address this gap by promoting consistency and harmonization in integrated response assessment.

Drs. Przepiorka and Jen express concern that integrated reporting may complicate data extraction and introduce inconsistency. We would like to emphasize that, in routine practice, the integrated diagnostic reports comprise individual test reports alongside a final interpretive summary. Thus, all primary data remain transparently accessible. We anticipate that our proposed algorithms will enhance, rather than complicate, standardization of reporting blast response across laboratories.

We have stated in our guidelines that morphological assessment of response remains essential for all bone marrows, whilst acknowledging its limitations that include the high coefficient of variation between hematopathologists. However, accurate quantitation of residual leukemic burden, particularly for those with blasts below 5%, requires measurable residual disease (MRD) assays in accordance with established acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) recommendations(3-9). Importantly, our recommendations do not conflate remission with MRD-negative endpoints. As illustrated in Figures 1 and 2 of *Wang et al*, patients with <5% bone marrow blasts but positive for MRD as well as patients with an MRD negativity (defined by <0.01% for ALL and at least <0.1% for AML) both meet the criteria for bone marrow remission. This reflects the biological continuum of response with MRD negativity representing the most stringent endpoint.
A key objective of our recommendations is to prevent clinically relevant misclassification. For example, patients with $\geq$ 5% apparent bone marrow blasts due to normal left-shifted myeloid regeneration or hematogone expansion, but who are MRD-negative by validated assays, should not be categorised as refractory or relapsed. Avoiding such misclassification is critical for appropriate clinical decision-making, both within and outside clinical trials. As emphasised in our recommendations, MRD results must always be interpreted in the context of sample quality and potential target limitations, particularly in cases of discordant findings across platforms.

We agree that in AML, only morphology and flow cytometry provide quantitative estimates of blasts whilst molecular MRD methods detect cells derived from the leukemic clone independently of maturation stage or viability. This is a particular consideration in AML due to increasing use of differentiation-inducing therapies. There are other reasons why molecular MRD assays are unsuitable for deriving leukemic cell percentages in AML. RNA based PCR assays of AML-defining genetic abnormalities measure target transcripts that are variably expressed in leukemic cells whilst gene mutations monitored by DNA- based assays may be subclonal (such as *FLT3* mutations) or pre-leukemic (such as *IDH* mutations). Therefore, in our recommendations, only flow cytometry and /or morphology should be used to report blast percentage in AML for MRD positive bone marrows. In

contrast, in ALL, similarly to myeloma and CLL, DNA based molecular assays targeting clonal immunoglobulin and or T cell receptor gene rearrangements provide direct quantitation of leukemic cells. These molecular MRD tests as well as flow cytometric MRD take precedence over morphology for reporting remission (<5% blasts) across trial groups(3, 4). Our guidelines as displayed in Figure 1 are aligned with this and aim to ensure consistency in reporting.

We welcome further continued dialogue with Drs Przepiorka, Jen and their colleagues at the FDA. Input of regulatory agencies is critical for achieving international harmonization of response criteria and ensuring alignment between clinical trial reporting and routine clinical practice for categorising remissions and relapses. Their suggestion to move towards single platform flow cytometric blast enumeration, is an important area for future development. In ALL, this would require careful evaluation of its added value to the recommended molecular assays, particularly in the context of resource implications and variable access to standardised testing. We agree that flow cytometric monitoring should be performed in all AML patients in parallel with morphology and the ELN recommended molecular MRD tests. Although reliance on a single assay offers operational simplicity, it risks obscuring assay specific limitations that differ across samples and patients. While concordance between the results of different platforms is the more frequent result of integrated reporting, the intentional arbitration of discordance improves accuracy and adds confidence in data quality. Hence it is likely that integrated reporting will continue as the benchmark.
Ultimately, robust qualification of the appropriate assays for measuring blasts /leukemic cells at clinically relevant thresholds such as the 5% remission cutoff will benefit from continued interlaboratory laboratories comparison through external quality assurance programs.

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