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Bone marrow biopsy characteristics at nadir after intensive induction therapy do not predict outcomes in adult acute myeloid leukemia patients: an analysis of ECOG-ACRIN clinical trials

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DT, CG, EA and SL conceptualized the study. LS and ZS performed the statistical analysis. HG, JF, DAA, HL, YZ, EP, JMB, JR, ML, EA and SL performed the clinical trials. DT wrote the manuscript which was reviewed, edited and approved by all authors.

Data Sharing Statement
Data sets generated and/or analyzed during the current study may be available from the corresponding author upon reasonable request.

To the editor:

In acute myeloid leukemia (AML) patients treated with intensive cytarabine-based induction therapy, present guidelines often recommend an interim bone marrow biopsy (BM Bx) to be performed 14-21 days after initiation of therapy to assess early responsiveness to induction chemotherapy (1). In the presence of residual disease, defined as an elevated marrow cellularity ≥20% and/or blast counts ≥5%, a second cycle of chemotherapy is frequently given at nadir to induce a complete response. Although the prognostic value of an interim BM Bx has been questioned by multiple analyses (2-7), the presence of continued disease is still frequently used to justify additional therapy at this interim time point. The benefit of this approach has never been confirmed and with the advent of effective less-intensive therapeutic options, including hypomethylating agents with venetoclax (HMA-VEN), the utility of additional intensive reinduction chemotherapy is furthermore called into question. We hypothesized that characteristics of the nadir BM Bx, such as degree or change in disease burden, may predict eventual response to reinduction therapy. To evaluate this, we analyzed data from ECOG-ACRIN clinical trials in AML of intensive induction chemotherapy with nadir biopsy information available to determine predictors of outcomes after reinduction.

We included patients from ECOG-ACRIN AML studies treated with intensive chemotherapy with granular nadir bone marrow biopsy data (E1900 trial and Arm A of E2906) (8, 9). Patients were enrolled in E1900 between 2002 and 2008, and in E2906 between 2011 and 2019. Induction therapy consisted of cytarabine 100mg/m^2 days 1-7 with daunorubicin 45mg/m^2 or 90mg/m^2 days 1-3 in younger adults on E1900 or 60mg/m^2 days 1-3 in older adults on Arm A of E2906. We defined nadir biopsy as the first biopsy to occur during induction therapy, which was commonly performed on day 14. Residual disease was defined as blasts ≥5% (assessed by morphologic assessment of aspirate) or cellularity ≥20% to align with both trial protocols and

current National Comprehensive Cancer Network guideline recommendation (1). Per study protocols, patients with residual disease were to receive a second cycle of induction chemotherapy with cytarabine 100mg/m^2 days 1-7 and daunorubicin 45mg/m^2 days 1-3 (E1900) or 60mg/m^2 days 1-3 in Arm A of E2906, if considered safe. The present analysis focuses on subjects who had residual disease on nadir biopsy and received reinduction therapy. This analysis was conducted using data from E1900 and E2906, both of which were approved by institutional review boards at participating sites in accordance with the Declaration of Helsinki.

Of 1013 AML patients included across both studies, patients were excluded for missing nadir biopsy information (N=192), lack of strictly defined residual disease at nadir (N=209) or not having received reinduction therapy despite residual disease (N=279), leaving a final study population of 233 patients. The baseline characteristics are shown in **Table 1.** The median age was 58 with 42% female. Initial induction therapy consisted of cytarabine 100mg/m^2 with daunorubicin 45mg/m^2 in 81 patients (34.8%), 60mg/m^2 in 97 patients (41.6%) and 90mg/m^2 in 55 patients (23.6%). The median baseline bone marrow morphologic blast percentage was 57% (8-100%).

Among the cohort of patients receiving reinduction therapy, 118 patients (52%) achieved a complete remission (CR, CR with incomplete count recovery was not consistently collected in E1900 and E2906 and is not included). The median OS for the entire population was 14.2 months (95% confidence interval [CI]: 10.7–17.1 months). The 30-day mortality from induction or reinduction was 5.2%.

The median time from baseline to nadir biopsy was 13 days (range 11-20) among the 233 patients with residual disease and receiving reinduction therapy. The median bone marrow blast percentage at nadir was 30% (0-97%) and 96.9%, 86.4% and 64.9% of patients had blasts

≥5%, 10% and 20%, respectively. From baseline to nadir biopsy, there was a median change in blast percentage by -15% (range -95% - +66%). The median change in blast percentage from baseline to nadir in those who achieved a CR was -21% compared to -11% in those who did not achieve a CR (**Figure 1**), a difference which was not significant (p=0.081).

Logistic regression adjusting for baseline blast percentage found no association between either absolute (odds ratio [OR] 0.993, 95%CI 0.984-1.003, p=0.20) or relative blast percentage difference (OR 0.998, 95% CI 0.994-1.002, p=0.33) and achieving CR. Similarly, there was no significant association between achieving any reduction in blast percentage from baseline to nadir and CR (OR 1.283, 95%CI 0.948-1.740, p=0.11). Finally, evaluating by cytogenetics risk similarly did not show any significant association between absolute or relative change in bone marrow blasts and CR. Similarly, there was no association between absolute, relative, or any change in bone marrow cellularity from baseline to nadir and CR.

We next evaluated the association between relative blast change and both OS and DFS using Cox proportional hazard model adjusting for baseline blasts. Similarly, there was no impact of relative bone marrow blast change on OS (hazard ratio [HR] 0.808, 95% CI 0.580-1.126, p=0.21) or DFS (HR 0.743, 95% CI 0.506-1.091, p=0.13). Similar results were seen for each cytogenetic risk group separately. To address potential confounding by induction intensity, we repeated our primary models with study protocol (E1900 vs. E2906), a surrogate for daunorubicin dose, included as a covariate. Results were materially unchanged across all endpoints, and protocol was not independently associated with CR, OS, or DFS (all p>0.15).

Our study has several limitations which are important to acknowledge. Firstly, the reason for not pursuing reinduction therapy in the presence of residual disease was not captured in the dataset. Specifically, out of 512 patients with protocol-defined refractory disease at nadir, 279

(54%) did not receive reinduction therapy. Among all patients with protocol-defined residual disease at nadir (n=512), median OS was 15.4 months (95% CI, 13.4–18.2) and median DFS was 11.9 months (95% CI, 10.1–13.3), with numerically longer OS (17.3 vs. 14.2 months) and DFS (12.8 vs. 10.7 months) among patients who did not receive reinduction compared with those who did. Patients not receiving reinduction therapy were older (64 vs 58 years, $p<0.001$), had less adverse cytogenetic risk (23% versus 32%, $p=0.024$), had a significantly lower median nadir blast percentage (4% versus 30%, $p<0.001$) and higher median nadir cellularity (40% versus 20%, $p<0.001$) as compared to patients with residual disease who did receive reinduction therapy (**Supplementary Table 1**). These differences suggest a more favorable response to initial induction that may have led many providers and/or patients to not proceed with a second cycle of induction because of lack of elevated blasts despite elevated cellularity. It is also possible that additional intensive reinduction therapy may not be necessary to induce a CR. Previous reports have noted that many patients with residual disease at nadir may go on to achieve a CR without additional chemotherapy (10).

Because our cohort is restricted to patients selected who went on to receive reinduction, our findings speak to the prognostic value of nadir biopsy characteristics within that selected population, not to whether morphologic residual disease itself warrants reinduction, a question our data cannot address given this selection. Whether reinduction itself, independent of nadir biopsy characteristics, improves outcomes among patients with residual disease could not be determined in this analysis given the unmeasured and likely heterogeneous reasons underlying the reinduction decision; this warrants dedicated study in future work.

An additional important limitation is the lack of uniform mutational information preventing us from adjusting for genetic risk status, which greatly impacts chemotherapy responsiveness; we cannot exclude the possibility that unmeasured molecular risk contributes to our negative

finding. Although we could not directly assess molecular risk in this cohort, its established prognostic significance in AML supports incorporating it into reinduction decisions independent of the morphologic findings reported here. Measurable residual disease assessment was also not universally available for participants in these trials.

Bone marrow biopsies were also reviewed locally without central review. While sample size of the reinduction analysis was powered to detect moderate-to-large effects, smaller associations cannot be excluded. Finally, the post-hoc nature of this analysis does not allow us to compare a second induction cycle with alternative salvage options (e.g. HMA-VEN).

In conclusion, this analysis of 233 patients across two ECOG-ACRIN AML clinical trials treated with intensive induction therapy demonstrates that nadir biopsy – including absolute blast percentage, relative blast change and cellularity – failed to predict CR, OS, or DFS. These findings may reflect intrinsic biological properties of the leukemia — such as proliferative kinetics, microenvironmental interactions, or resistance mechanisms — that are not captured by morphologic assessment alone. Our results suggest that the morphologic findings of residual disease at nadir biopsy should not be the primary driver of reinduction decisions. Rather, patient fitness, cytogenetic and molecular risk, and the availability of alternative salvage strategies such as HMA-VEN should be integrated into shared decision-making at this critical juncture. While prospective studies directly comparing intensive reinduction to alternative salvage strategies in this population are warranted, the feasibility of performing such a study may be difficult.

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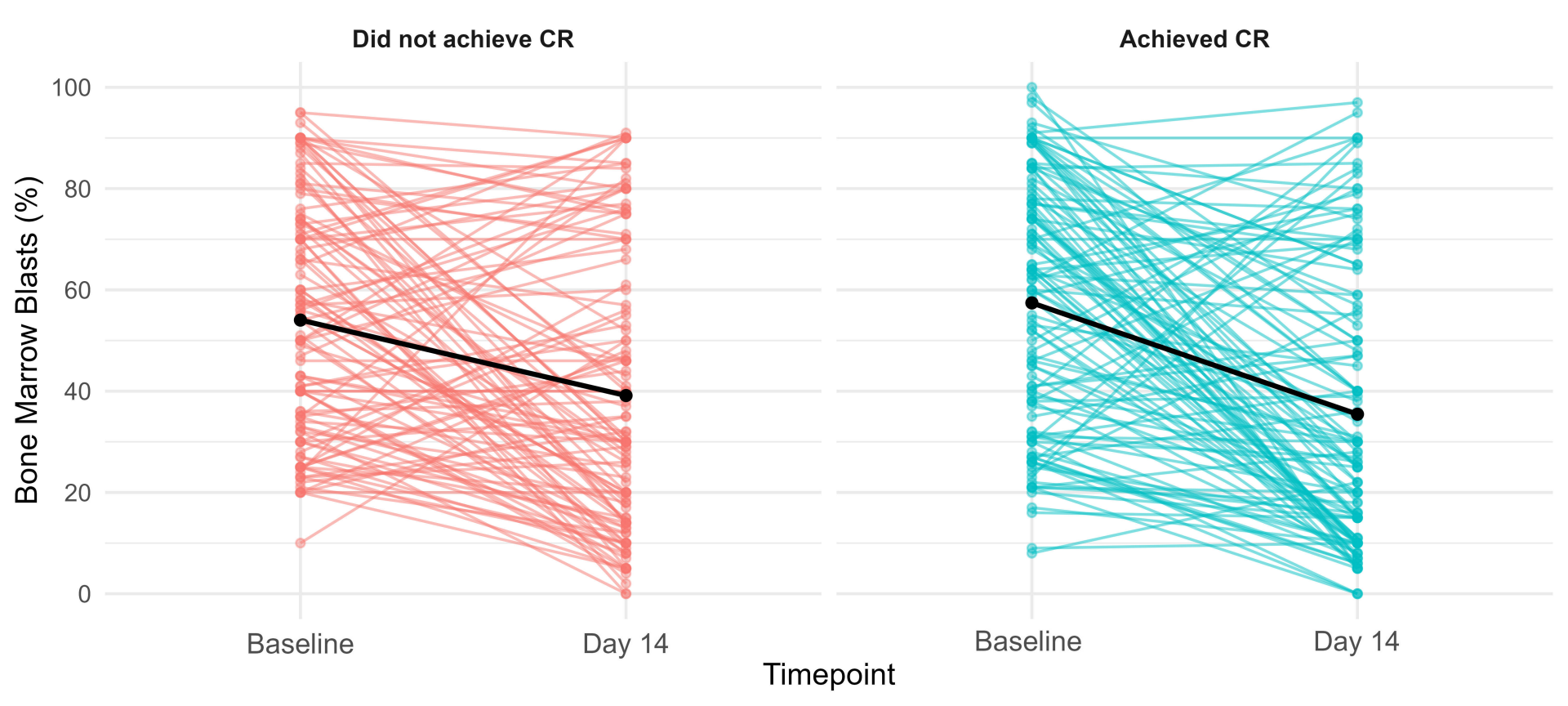
Table 1. Baseline characteristics

	Overall, N = 233
Age (years), median (range)	58 (18-78)
Sex, N (%)	
Female	97 (42.0%)
Male	134 (58.0%)
Cytogenetics (ELN2017), N (%)	
Favorable	5 (2.7%)
Intermediate	123 (66.5%)
Adverse	57 (30.8%)
Unknown	48
Induction treatment received, N (%)	
Daunorubicin 45mg/m^2 D1-3 Cytarabine 100mg/m^2 D1-7	81 (34.8%)
Daunorubicin 60mg/m^2 D1-3 Cytarabine 100mg/m^2 D1-7	97 (41.6%)
Daunorubicin 90mg/m^2 D1-3 Cytarabine 100mg/m^2 D1-7	55 (23.6%)
Reinduction treatment received, N (%)	
Daunorubicin 45mg/m^2 D1-3 Cytarabine 100mg/m^2 D1-7	136 (58.4%)
Daunorubicin 60mg/m^2 D1-3 Cytarabine 100mg/m^2 D1-7	97 (41.6%)
Bone marrow blast at baseline, median (range)	57% (8 - 100%)
Bone marrow cellularity at baseline, median (range)	90% (0 - 100%)

D = day, ELN = European LeukemiaNet

Figure Legends

Figure 1. Change in bone marrow blast percentage per patients from baseline to nadir stratified by response. Each line represents an individual patient. Those who obtained a post reinduction CR had a median change in blast percentage from baseline to nadir of -21% compared to -11% in those who did not achieve a CR, which was not significantly different (p=0.081).


Did not achieve CR
Achieved CR
Bone Marrow Blasts (%)
100
80
60
40
20
0
Baseline
Day 14
Baseline
Day 14
Timepoint

Supplementary Table 1.

	Reinduction (N=233)	**No-reinduction (N=279)**	**p-value**
Age (years), median (range)	58 (18-78)	64 (20-83)	<0.001
Sex, N (%)			0.5
Female	97 (42.0%)	125 (45.3%)	
Male	134 (58.0%)	151 (54.7%)	
Cytogenetics (ELN2017), N (%)			0.067
Favorable	5 (2.7%)	15 (6.5%)	
Intermediate	123 (66.5%)	162 (70.1%)	
Adverse	57 (30.8%)	54 (23.4%)	
Unknown	48	48	
Nadir BM blast ≥5%, N (%)	221 (96.9%)	135 (49.6%)	<0.001
Nadir BM blast ≥10%, N (%)	197 (86.4%)	93 (34.2%)	<0.001
Nadir BM blast ≥20%, N (%)	148 (64.9%)	75 (27.6%)	<0.001
Nadir BM cellularity ≥20%, N (%)	119 (56.7%)	224 (85.2%)	<0.001
Basis for residual disease, N (%)			<0.001
BM blasts ≥5% alone	114 (48.9%)	55 (19.7%)	
Cellularity ≥20% alone	12 (5.2%)	144 (51.6%)	
Both	107 (45.9%)	80 (28.7%)	
30-day mortality (from nadir biopsy), N (%)	12 (5.2%)	16 (6.0%)	0.7