THE PROGNOSTIC VALUE OF DAY 14 BONE MARROW BLAST CLEARANCE IS MUTATION-DEPENDENT IN NEWLY DIAGNOSED, INTENSIVELY TREATED ACUTE MYELOID LEUKEMIA (AML)

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INTRODUCTION

Assessment of bone marrow blast clearance at day 14 (D14) is routine during intensive AML induction, yet its prognostic value, and its usefulness for deciding which patients require a second induction, remains uncertain. Molecularly defined subgroups may differ in how quickly blasts clear[1], so a single D14 threshold may not be universally prognostic across all patients.

AIM

To compare the prognostic role of D14BM across mutation subgroups in an AML cohort treated with intensive chemotherapy.

METHODS

We analysed 428 patients with AML treated in the PALG-AML/2016 trial with DA-90 or DAC induction; all had an assessable D14 marrow. Outcomes were composite complete remission (cCR, i.e. CR/CRi after up to two inductions), overall survival (OS) and event-free survival (EFS), with time zero at randomisation.

Mutation × D14 interactions were tested for each outcome. Youden's index identified the optimal D14 blast cutoff for cCR failure, overall and within each subgroup. Kaplan–Meier analysis and Cox models were applied at the subgroup-tailored cutoffs. A sensitivity analysis excluded patients who received a second induction.

RESULTS

cCR was achieved in 318/428 patients (74%). Rates differed markedly by molecular subgroup (Figure 1).

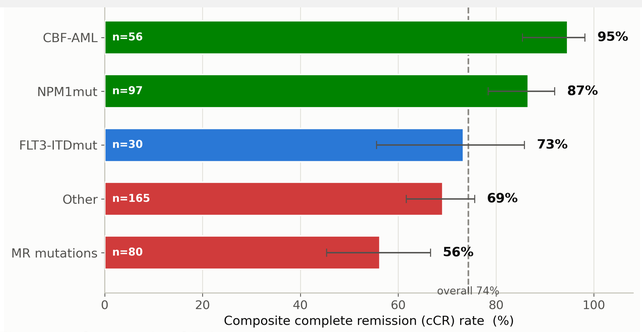

Figure 1. Composite CR by molecular subgroup

RESULTS (CONTINUED)

Delayed clearers (D14 >5%) were enriched for adverse genetics: myelodysplasia-related (MR) mutations, *TP53*^{mut} and *RUNX1*^{mut} (OR 1.90) — and depleted of favourable-kinetic lesions: *NPM1*^{mut} and CBF-AML (Figure 2). Nearly 12% of patients received second induction, including 37% of those without a D14 <5% blast clearance.

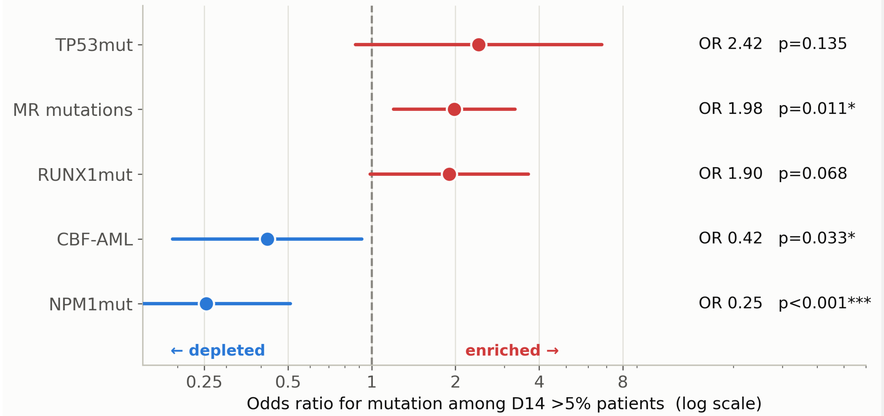

Figure 2. Molecular enrichment among delayed clearance patients (D14 >5%).

D14 >5% was a strong negative predictor of cCR, OS (HR 2.0, 95%CI 1.5-2.7) and EFS (HR 2.5, 95%CI 1.9-3.3; both p<0.001) overall, but was not prognostic for *FLT3-ITD*^{mut} (OS and EFS interaction p=0.002) or *RUNX1*^{mut} (cCR interaction p=0.011, EFS interaction p=0.10; Figure 3). The optimal blast cutoff for the overall population for cCR was 5%; no alternative cutoff achieved prognostic value in *FLT3-ITD*^{mut} or *RUNX1*^{mut} patients. At a common 5% cutoff, Kaplan–Meier analysis confirmed that D14 was not prognostic for OS or EFS in *FLT3-ITD*^{mut} or *RUNX1*^{mut} patients (Figure 4); this was robust in a sensitivity analysis restricted to patients who did not receive a second induction (n = 377). A potential subgroup-specific cutoff of 12% was prognostic in *TET2*^{mut} AML (HR 5.7, 95%CI 2.0-16.5 for OS), but the analysis was limited by small sample size.

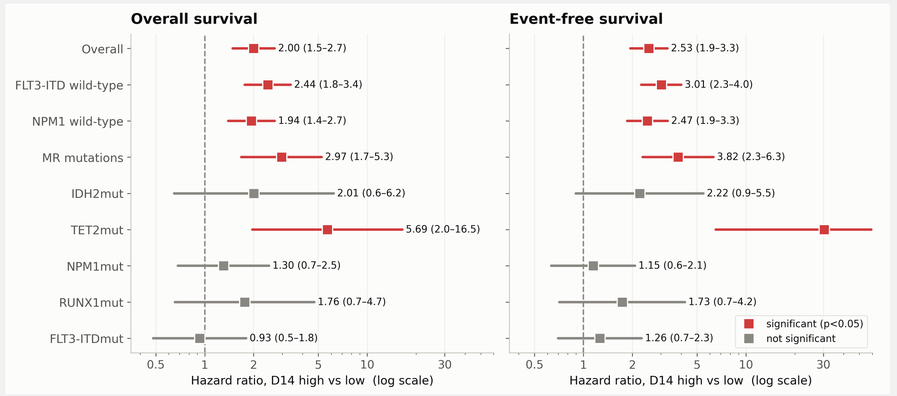

Figure 3. Prognostic significance of D14 blast clearance across subgroups at tailored cutoffs.

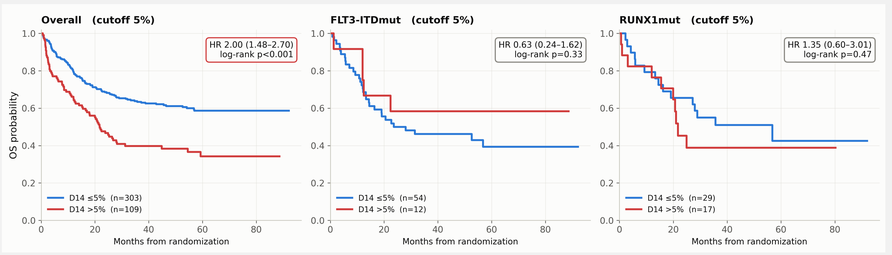

Figure 4. Overall survival categorized by 5% blast clearance at D14 among all patients, patients with *FLT3-ITD* mutation and patients with *RUNX1* mutation.

CONCLUSIONS

- D14 clearance is a strong predictor of remission and survival (D14 >5%: OS HR 2.0, EFS HR 2.5; both p<0.001), robust to adjustment for age, ELN2022 risk and second induction.
- Its value is subgroup-dependent: D14 is NOT prognostic in FLT3-ITD– or RUNX1-mutated AML.
- Early marrow response should be read in molecular context, not by one universal threshold.

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