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Received: 29 May 2026 | Accepted: 4 September 2026

DOI: 10.1111/bjh.70874

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Haematological Malignancy – Clinical

Increase in fetal haemoglobin from baseline to day 10 is a biomarker for response to decitabine in AML: Results of the AML21 randomized phase III trial of the EORTC Leukemia Group, Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and German MDS Study Group

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Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: SFB 992 C04; Astellas Pharma; Bristol-Myers Squibb; Immunocore; Johnson and Johnson; MSD; Pierre Fabre; Janssen Pharmaceuticals

Summary
Lack of response or delayed response to therapy are major challenges in the use of DNA-hypomethylating agents (HMA) in patients with acute myeloid leukaemia (AML). Fetal haemoglobin (HbF) is a potential biomarker for response to HMA treatment but has only been studied in small single-centre studies. We investigated the association between HbF and treatment outcome in the randomized phase 3 European Organisation for Research and Treatment of Cancer (EORTC)-1301 trial AML21, which included 606 fit, older AML patients who received 10-day decitabine or '3 + 7' chemotherapy as induction. HbF was measured twice in the decitabine arm ($n = 135$) and at baseline in the 3 + 7 arm ($n = 97$). In the decitabine arm, HbF increase from baseline to day 10 was associated with increased odds of reaching complete remission (CR) or CR with incomplete count recovery (CRi) (odds ratio [OR] 2.40, 95% confidence interval [CI] 1.15–5.02, $p = 0.020$). The hazard ratio (HR) for death comparing patients with HbF increase to those without was 0.83 (95% CI 0.55–1.28, $p = 0.40$). Baseline HbF in the decitabine arm was not associated with CR/CRi (OR 0.89, 95% CI 0.45–1.75, $p = 0.73$) or overall survival (HR 0.86, 95% CI 0.58–1.28, $p = 0.47$). In conclusion, this large prospective study adds to the body of evidence that HbF is an easy-to-measure early biomarker for response to HMA treatment.

KEYWORDS
adverse-genetics AML, de-escalation, HbF, hypomethylating agents

For affiliations refer to page 7.

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INTRODUCTION

DNA-hypomethylating agents (HMA) are commonly used to treat patients with acute myeloid leukaemia (AML) who are unable or unwilling to receive intensive chemotherapy.

However, about half of the patients receiving HMA fail to respond and treatment responses are often delayed.[1,2] Therefore, better outcome predictors are needed.[3]

The expression of gamma-globin genes is regulated by DNA methylation, and HMA treatment increases gamma-globin synthesis in patients with haemoglobinopathies, resulting in increased fetal haemoglobin (HbF) levels.[4,5] While HbF has also been studied in patients with myeloid neoplasms for some time,[6] several recent reports suggest that HbF might help to predict outcome in patients with AML or myelodysplastic neoplasms (MDS) treated with HMA. In studies of pre-treatment HbF, patients with elevated compared to normal HbF levels in peripheral blood erythrocytes had superior outcome following decitabine or azacitidine treatment.[7,8] HbF induction during HMA treatment was also shown to be associated with better response and survival.[9,10] These previous studies, however, were limited by small sample sizes and studies with HbF measurements in larger cohorts of patients with AML treated with HMA are lacking.

We hypothesized that baseline HbF and HbF measured shortly after decitabine treatment start are associated with outcome. We addressed this hypothesis in the European Organisation for Research and Treatment of Cancer (EORTC)-1301 trial AML21, an open-label, randomized, controlled phase 3 trial which included 606 older patients with AML who received decitabine treatment or 3 + 7 chemotherapy and had HbF measured at baseline and day 10 of treatment.[11] Using this large cohort of patients, we sought to investigate HbF as a potential biomarker of response to decitabine treatment.

METHODS

Patients

HbF levels were determined in participants of the EORTC-1301 trial AML21, an open-label, randomized, controlled phase 3 trial conducted across nine European countries.[11] The trial enrolled patients aged ≥60 years with newly diagnosed AML, who were eligible for intensive chemotherapy. Patients in the decitabine arm received decitabine (20 mg/m^2 for 10 days in the first cycle and for 5 or 10 days every 28 days in subsequent cycles). Patients in the 3 + 7 chemotherapy arm received daunorubicin (60 mg/m^2 days 1–3) and cytarabine (200 mg/m^2 days 1–7), followed by 1–3 additional chemotherapy cycles.

The clinical cut-off date for this study was June 30, 2023. The study population included all patients for whom HbF data were available and who provided consent for biobanking.

The HbF project and the statistical analysis methods were prospectively planned.

Overall survival (OS) was defined as the time from randomization to death of any cause. The follow-up of patients who had not died before the clinical cut-off date was censored at the clinical cut-off date or last contact with the patient, whichever came first.

In the complete remission (CR)/CR with incomplete count recovery (CRi) analysis, achieving a CR/CRi before allogeneic haematopoietic stem cell transplantation (allo-HSCT) and as response to the protocol treatment was classified as a success. All remaining patients were classified as not having reached a CR/CRi.

The study was approved by the institutional review board of the University of Freiburg Medical Center. Written informed consent was obtained according to the Declaration of Helsinki.

Haemoglobin quantification

HbF was measured in ethylenediaminetetraacetic acid (EDTA)-anticoagulated blood by high-performance liquid chromatography[7,9,12] at the Central Laboratory of the University of Freiburg Medical Center. Blood samples from other study centres were shipped at room temperature to Freiburg Medical Center for HbF measurements.

Statistical methods

For all estimated parameters, 95% confidence intervals (CIs) were provided. All tests were performed at a significance level of 0.05 (two-sided). HbF increase was defined as any increase in HbF.

OS was described using the Kaplan–Meier approach. The log-rank test was used to compare OS between elevated and normal HbF. The hazard ratio (HR) from an unadjusted Cox model was used to summarize the difference between the two groups. Cox regression model was fitted among all patients with baseline data available to investigate whether the association between HbF at baseline and OS differed by treatment arm.

The Mann–Whitney test was used to investigate the association between HbF values or ratio and achieving CR/CRi. The odds ratio (OR) from an unadjusted logistic regression model was used to summarize the difference between elevated and normal HbF. A logistic regression model was used among all patients with baseline data available to investigate whether the association between HbF at baseline and achieving CR/CRi differed by treatment arm.

Regression models included treatment arm, baseline HbF and the interaction term as covariates.

Wilcoxon signed-rank test was used to investigate whether HbF values increased between baseline and day 10 in the decitabine arm.

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RESULTS

Patients

Between 2015 and 2019, a total of 606 patients with AML underwent randomization at 54 centres across Europe. A total of 303 patients each were randomly assigned to the decitabine arm and to the 3+7 chemotherapy arm (Figure 1). Three hundred and fifty-four patients overall were excluded from the HbF analysis, primarily because they were randomized before February 2017, which is when HbF measurements were initiated within the trial. Demographic and clinical characteristics were similar between patients who were included in the analysis and those who were not (data not shown).

Baseline HbF was measured in 152 patients in the decitabine arm and 97 patients in the 3+7 arm. In 135 patients in the decitabine arm, HbF was measured both at baseline and at day 10 of treatment.

Baseline demographic and clinical characteristics of patients with available HbF data were similar between the two treatment arms (Table 1). The median age of patients was 68 years in the decitabine arm and 69 years in the 3+7 arm. Most patients had de novo AML. Genetic abnormalities associated with adverse risk according to the 2022 European LeukemiaNet (ELN) recommendations[13] were present in 55.1% of the patients in the decitabine arm and 65.6% of those in the 3+7 arm.

An early HbF increase is associated with response to decitabine treatment

To investigate the association between decitabine-induced changes in HbF and outcome, HbF was measured at baseline and day 10 of treatment in patients in the decitabine arm. Among 135 patients in the decitabine arm who had HbF measured both at baseline and day 10 of treatment, the median difference between day 10 and baseline HbF was 0 ($p = 0.144$). Forty-six patients had an HbF increase between baseline and day 10 (median day 10 to baseline ratio of 1.75); 89 patients had no increase (median ratio of 0.80, Table S1). Demographic and clinical characteristics were similar between patients with an increase and patients without an increase in HbF (Table S1). To study changes in HbF as a potential biomarker of treatment response, we analysed the association between HbF change from baseline to day 10 of decitabine treatment and reaching CR or CRi. The ratio of day 10 to baseline HbF was higher in patients who reached CR/CRi than in those who did not (median ratio of 1 [Q1, 0.80; Q3, 1.33] and 0.86 [Q1, 0.67; Q3, 1.00], respectively, $p = 0.037$, Figure 2A). HbF increase from baseline to day 10 in the decitabine arm was associated with an increased odds of reaching CR/CRi in both unadjusted analysis (OR 2.40, 95% CI 1.15–5.02, $p = 0.020$, Table 2) and after adjusting for age, white blood cell count at diagnosis and sex (OR 2.51, 95% CI 1.17–5.38, $p = 0.018$, Table 3).

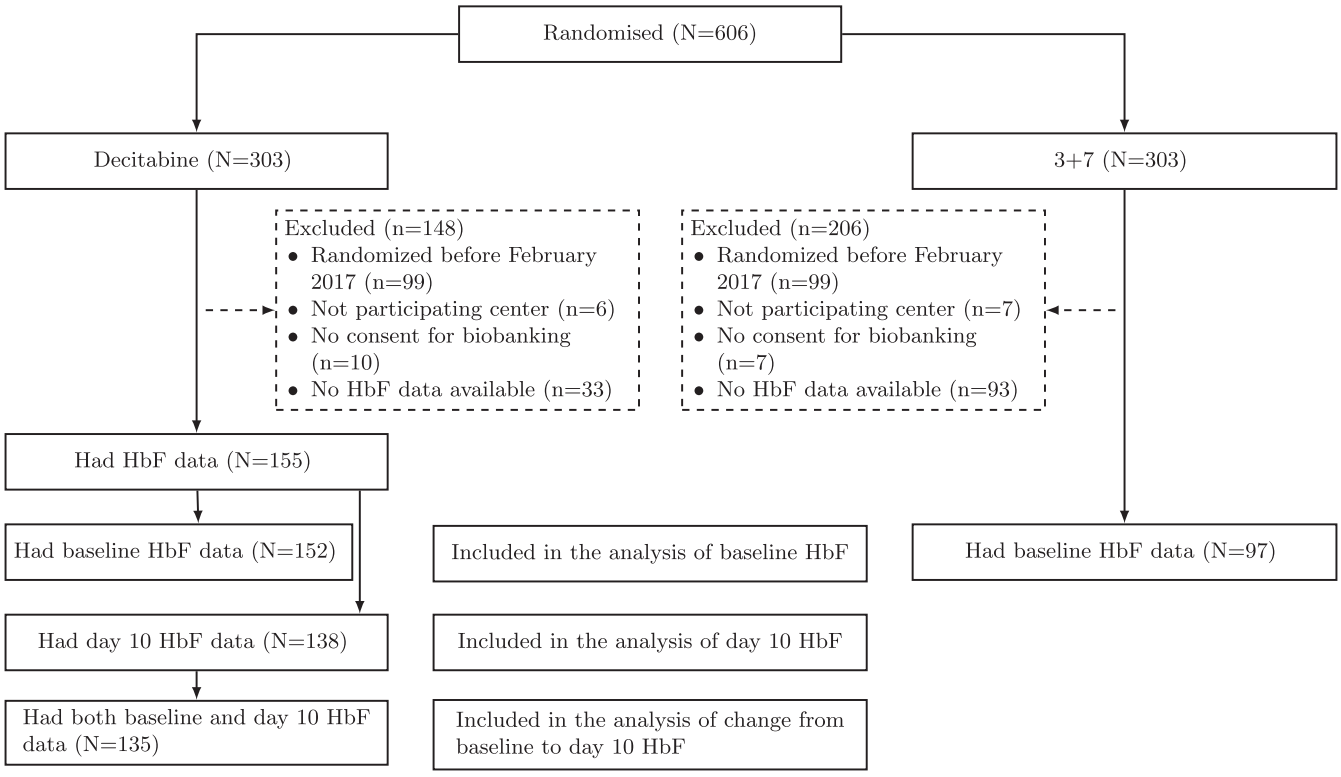

FIGURE 1 Workflow for selecting patients for HbF data analysis within the trial. Of 606 patients, 303 patients each were randomly assigned to the decitabine arm and to the 3+7 chemotherapy arm. HbF measurements were available in 155 patients in the decitabine arm and 97 patients in the 3+7 arm.

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TABLE 1 Characteristics of the patients at baseline.

Characteristic	Decitabine (*N* = 155)	3 + 7 (*N* = 97)
Age, years		
Median (range)	68 (60–80)	69 (60–81)
60–64, *N* (%)	35 (22.6)	20 (20.6)
65–69, *N* (%)	70 (45.2)	36 (37.1)
≥70, *N* (%)	50 (32.3)	41 (42.3)
Sex		
Patients with available data	155	95
Male, *N* (%)	82 (52.9)	62 (65.3)
Female, *N* (%)	73 (47.1)	33 (34.7)
ECOG performance status, *N* (%)		
0	88 (56.8)	45 (46.4)
1	56 (36.1)	46 (47.4)
2	11 (7.1)	6 (6.2)
White blood cells at diagnosis, 10^9/L, *N* (%)		
<5	82 (52.9)	58 (59.8)
≥5 and <30	47 (30.3)	27 (27.8)
≥30	26 (16.8)	12 (12.4)
AML type, *N* (%)		
Patients with available data	155	96
De novo	120 (77.4)	78 (81.3)
Secondary from MDS, MPN, or CMML	16 (10.3)	11 (11.5)
Therapy-related	19 (12.3)	7 (7.3)
Cytogenetics		
Patients with available data	137	88
Normal karyotype, *N* (%)	74 (54.0)	37 (42.0)
Abnormal karyotype, MK-, *N* (%)	43 (31.4)	40 (45.5)
MK+, *N* (%)	20 (14.6)	11 (12.5)
European LeukemiaNet 2022 risk group		
Patients with available data	136	90
Favourable, *N* (%)	36 (26.5)	9 (10.0)
Intermediate, *N* (%)	25 (18.4)	22 (24.4)
Adverse, *N* (%)	75 (55.1)	59 (65.6)

Abbreviations: CMML, chronic myelomonocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; MDS, myelodysplastic neoplasm; MK, monosomal karyotype; MPN, myeloproliferative neoplasm; *N*, number of patients.

The HR for death comparing patients with HbF increase between baseline and day 10 to those without was 0.83 (95% CI 0.55–1.28, $p = 0.40$, Figure 2B).

We also analysed the association between the HbF value measured on day 10 of decitabine treatment and outcome measures. Median day 10 HbF was 0.5%, unchanged from baseline. Of 138 patients in the decitabine arm with available day 10 HbF measurements, 45 had elevated HbF, defined as HbF >1%. Patient characteristics were similar between patients with elevated HbF and patients with normal day 10 HbF (Table S2). Median day 10 HbF in the decitabine arm was 0.6% in patients who reached CR/CRi and 0.4% in patients who did not ($p = 0.39$, Figure 2C). Day 10 HbF in the decitabine arm was not significantly associated with CR/CRi (OR 1.02 for elevated vs. normal, 95% CI 0.50–2.09, $p = 0.95$, Table 2) or OS (HR 0.95, 95% CI 0.62–1.45, $p = 0.81$, Figure 2D).

In summary, HbF levels remained overall stable in patients with AML after 10 days of decitabine treatment. An early increase in HbF following decitabine treatment may be a better predictor of response than a single timepoint HbF measurement early after treatment start.

Association between baseline HbF and outcome in the two treatment arms

We next assessed the association between baseline HbF and outcome in each treatment arm. In the decitabine arm, median HbF at baseline was 0.5% (Q1, 0.2%, Q3, 1.45%). Of 152 patients in the decitabine arm with available HbF measurements, 50 had elevated HbF at baseline. Patient characteristics were similar between patients with elevated HbF and patients with normal HbF at baseline (Table S3). Baseline HbF in the decitabine arm was comparable between patients who reached and who did not reach CR/CRi (median HbF = 0.5% and 0.45%, respectively; $p = 0.69$; Figure 3A). Baseline HbF was not significantly associated with CR/CRi (OR 0.89, 95% CI 0.45–1.75, $p = 0.73$; Table 2) or OS (HR 0.86, 95% CI 0.58–1.28, $p = 0.47$, Figure 3B) in the decitabine arm when comparing patients with elevated versus normal HbF.

In the 3 + 7 arm, median HbF at baseline was 0.3% (Q1, 0.05%, Q3, 0.8%). Of 97 patients in the 3 + 7 arm, 20 had elevated HbF at baseline. Patient characteristics in the 3 + 7 arm were similar between patients with elevated HbF and patients with normal HbF at baseline (Table S4).

Baseline HbF in the 3 + 7 arm was similar between patients who reached and who did not reach CR/CRi (median HbF = 0.4% and 0.25%, $p = 0.42$; Figure 3C). Baseline HbF in the 3 + 7 arm showed no evidence of an association with CR/CRi (OR 0.89, 95% CI 0.32–2.51, $p = 0.83$; Table 2) or OS (HR 0.93, 95% CI 0.52–1.68, $p = 0.81$; Figure 3D) when comparing patients with elevated versus normal HbF.

To investigate the possibility that, in the decitabine arm, the prognostic value of baseline HbF could have been different if the patients in the trial had not undergone allo-HSCT, a supplementary analysis using inverse probability of censoring weighting was used, censoring observations at the minimum of the censoring time in the main analysis and the time of allografting, and considering remission status as a time-varying confounder.[14] The model indicated no evidence of an association between baseline HbF and OS in the hypothetical scenario where no allografting had been performed (HR = 1.04, 95% CI 0.56–1.95, for elevated vs. normal).

Taken together, we did not detect an association between baseline HbF and treatment response or OS in either treatment arm. However, the direction of the associations between baseline HbF and CR/CRi or OS was consistent with previous reports.

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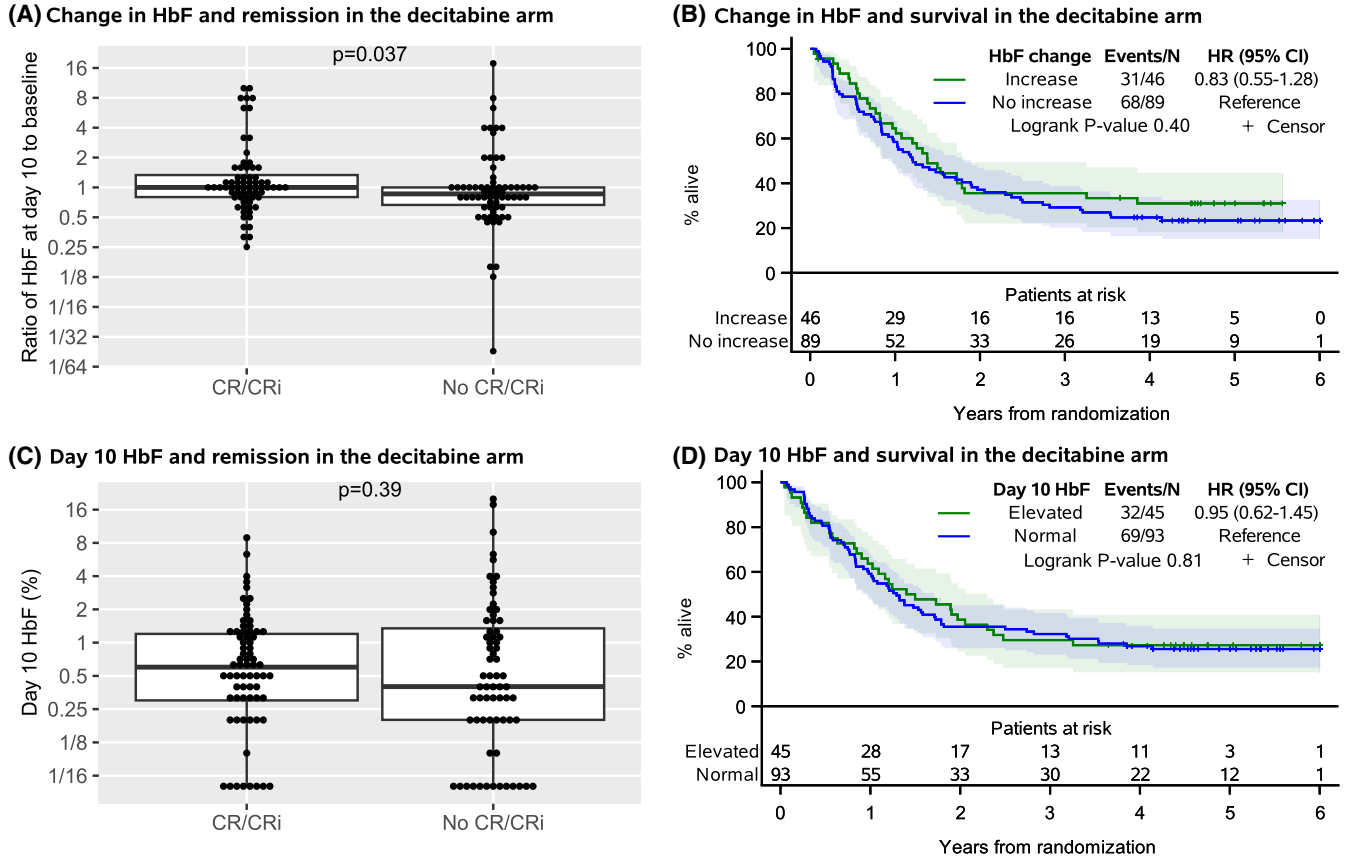

FIGURE 2 HbF increase between baseline and day 10 is associated with improved response to decitabine treatment. (A) Response to protocol treatment was analysed by ratio of HbF at day 10 to baseline in the decitabine arm. A total of 69 patients with both baseline and day 10 HbF data reached CR/CRi; 66 patients did not. (B) OS was analysed by change in HbF from baseline to day 10 in the decitabine arm. (C) Response to protocol treatment was analysed by HbF at day 10 in the decitabine arm. (D) OS was analysed by HbF at day 10 in the decitabine arm. (A, C) Each dot represents one observation (patient). The vertical lines connect the lowest and the highest values, the thick horizontal line indicates the medians, and the boxes indicate the first and the third quartiles. *p*-values for the difference between patients who reached and did not reach CR/CRi are displayed. (B, D) HR from an unadjusted and unstratified Cox model is displayed.

TABLE 2 Unadjusted analyses of the association between binary HbF indicators and response.

HbF indicator	CR/CRi *N* (row %)	No CR/CRi *N* (row %)	OR of CR/CRi (95% CI)	*p*-value
Change in HbF from baseline to day 10 in the decitabine arm				0.020
No increase	39 (43.8)	50 (56.2)	1	
Increase	30 (65.2)	16 (34.8)	2.40 (1.15–5.02)	
Day 10 HbF in the decitabine arm				0.95
Normal	47 (50.5)	46 (49.5)	1	
Elevated	23 (51.1)	22 (48.9)	1.02 (0.50–2.09)	
Baseline HbF in the decitabine arm				0.73
Normal	52 (51.0)	50 (49.0)	1	
Elevated	24 (48.0)	26 (52.0)	0.89 (0.45–1.75)	
Baseline HbF in the 3 + 7 arm				0.83
Normal	52 (67.5)	25 (32.5)	1	
Elevated	13 (65.0)	7 (35.0)	0.89 (0.32–2.51)	

Note: For each covariate, a separate logistic regression model was used. OR >1 indicates a higher probability of reaching CR/CRi.

DISCUSSION

Despite the routine use of HMA in AML and MDS for two decades, there is still a dearth of biomarkers predicting response to these epigenetically active agents. Elevated HbF was explored as a rational candidate already in 1982, when Ley et al. demonstrated in vivo induction of HbF, with concomitant hypomethylation of the gamma-globin promoter region, in a

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TABLE 3 Adjusted analysis of the association between HbF change from baseline and response.

Variable	OR of CR/CRi (95% CI)	*p*-value
HbF change		0.018
No increase	1	
Increase	2.51 (1.17–5.38)	
Age, years		
60–64	1	
65–69	0.54 (0.21–1.37)	
≥70	0.47 (0.17–1.31)	
White blood cells at diagnosis, 10^9/L		
<25	1	
≥25 and <50	0.98 (0.27–3.53)	
≥50	1.20 (0.37–3.87)	
Sex		
Male	1	
Female	1.22 (0.60–2.50)	

Note: Logistic regression model with covariates displayed in the table was used. OR >1 indicates a higher probability of reaching CR/CRi. A total of 135 patients were included in the analysis.

thalassaemia patient.[4] Clinical development of azacitidine and decitabine for patients with haemoglobinopathies followed but was eventually halted due to concerns regarding mutagenicity. Recent preclinical data suggest that HbF is also induced by an orally bioavailable, reversible DNMT1 inhibitor that is not incorporated into DNA.[15]

As the quantification of fetal haemoglobin can be routinely performed and is inexpensive, it would lend itself perfectly as a biomarker. Therefore, several groups committed to the development of low-cytotoxic, epigenetic treatment approaches have implemented serial HbF determination in their clinical trials of HMA-based treatments of myeloid malignancies.

We had retrospectively studied, in a single-centre analysis, two cohorts of older patients, ineligible for induction chemotherapy, receiving decitabine first-line therapy[7,9]: a higher-risk MDS cohort (EORTC phase III trial 06011, 16 patients) and an AML cohort (FR00331 single-arm phase II trial, 36 patients), serially assessing HbF as a potential biomarker. HbF was induced in patients from both cohorts, allowing outcome analyses which pointed towards HbF upregulation as an indicator for haematological treatment response and longer OS.[9] Interestingly, HbF levels that were already elevated prior

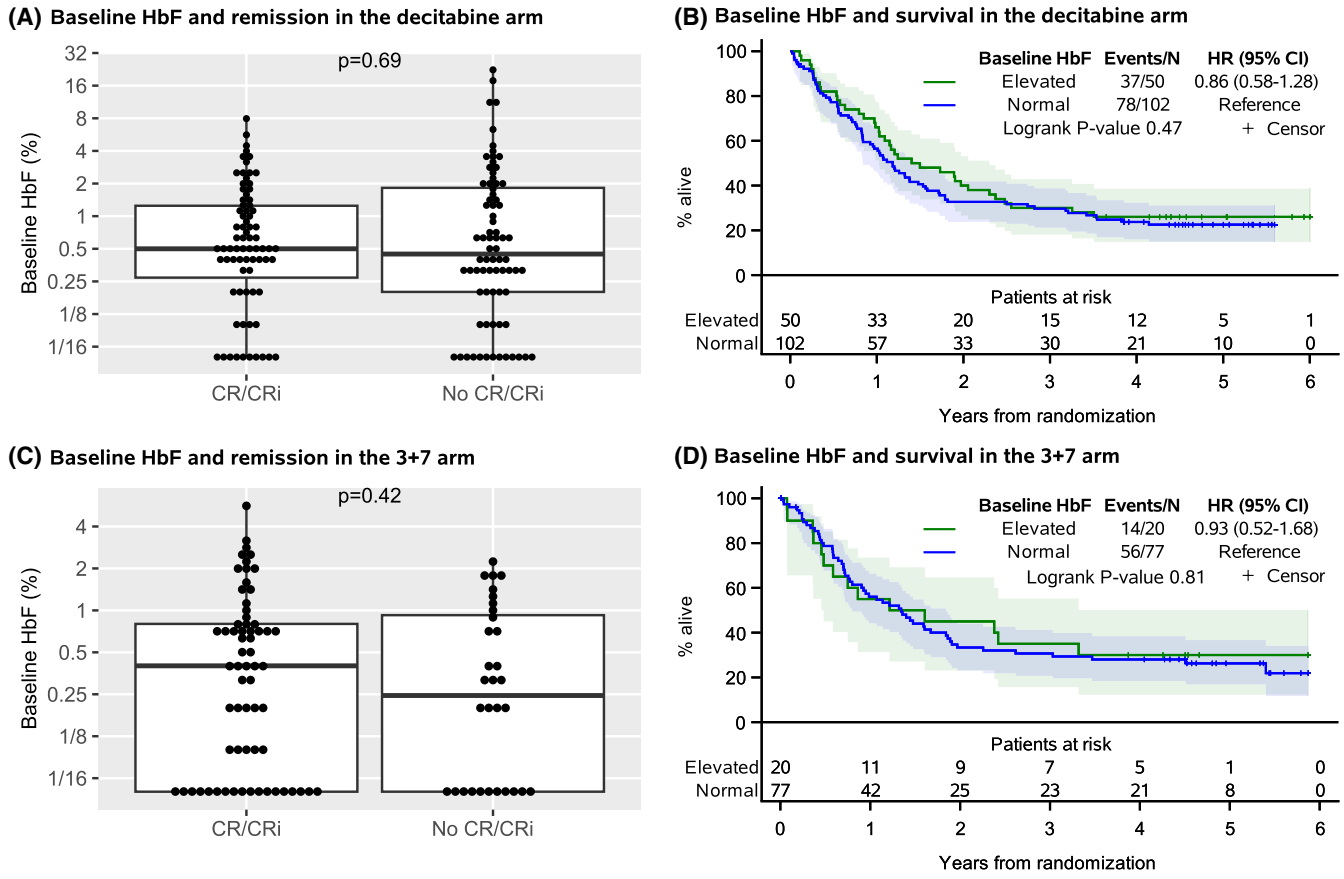

FIGURE 3 Association between baseline HbF and outcome in the two treatment arms. (A) Response to protocol treatment was analysed by HbF at baseline in the decitabine arm. A total of 76 patients with baseline HbF data each reached CR/CRi or not. (B) OS was analysed by HbF at baseline in the decitabine arm. (C) Response to protocol treatment was analysed by HbF at baseline in the 3 + 7 arm. (D) OS was analysed by HbF at baseline in the 3 + 7 arm. (A, C) Each dot represents one observation (patient). The vertical lines connect the lowest and the highest values, the thick horizontal line indicates the medians, and the boxes indicate the first and the third quartiles. *p*-values for the difference between patients who reached and did not reach CR/CRi are displayed. (B, D) HR from an unadjusted and unstratified Cox model is displayed.

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to treatment start also appeared to have prognostic value in both cohorts as elevated pre-treatment HbF was associated with longer median OS.[7] Hence, in the present, prospectively planned analyses, the goal was to validate these single-centre results in a large multicentre trial ensuring good data and sample quality.

As regards HbF induction by HMA treatment, a comparison between pre-treatment and day 10 from decitabine start was performed. In the 3 + 7 arm, HbF was measured only at baseline because HbF levels remain stable during treatment with cytarabine.[7] In the decitabine arm, HbF increase from baseline to day 10 was associated with increased odds of reaching CR/CRi; no statistically significant association between HbF induction and OS was detected. As day 10 of treatment is very early in the treatment course, it is possible that HbF induction on day 28 or 56 of decitabine treatment has a stronger association with outcome.

Regarding baseline HbF levels and outcome, the differences observed regarding CR/CRi rate and OS by trend supported the initial hypothesis, with estimated 1- and 2-year OS appearing higher in patients with elevated HbF receiving decitabine (but not 3 + 7). However, these analyses of baseline HbF were not statistically significant and because of the wide CIs fail to provide any conclusive evidence.

While increased baseline HbF potentially indicates a favourable prognosis in AML treated with decitabine,[7] increased HbF at diagnosis is associated with a poor prognosis in paediatric MDS.[16] In juvenile myelomonocytic leukaemia (JMML), HbF is produced by the malignant erythropoiesis.[17] In the subset of patients with *NRAS*-mutated JMML, normal to elevated HbF is associated with favourable outcomes,[18] suggesting that genetic and epigenetic disease features could be taken into account when considering HbF as a biomarker in leukaemias.

Limitations of this study include that some patients might have a haemoglobinopathy and that red blood cell transfusions might influence HbF levels. HbF measurements after cycle 1, 2 and later would have been ideal. However, the day 10 timepoint was chosen to match the acquisition of day 10 blood samples for in vivo demethylation studies in blasts.[11]

While change in HbF level after 10 days of treatment cannot help in the choice between HMA and intensive chemotherapy treatment, serial HbF determinations might help to guide clinical decisions such as the number of HMA treatment cycles.

Regarding the value of CR/CRi (ELN 2022[13]) after decitabine in the context of a bridge to transplant, long-term results of the AML21 trial were recently published.[19] Of 120 patients in the 10-day decitabine arm proceeding to allografting, with evaluable response at the start of conditioning, 28 (23%) were not in CR/CRi at time of transplant. Of 117 patients in the 3 + 7 arm, 10 (8.5%) were not in CR/CRi at time of transplant. OS from transplant was similar in the decitabine-treated patients irrespective of attainment of CR/CRi, whereas in patients having received 3 + 7, non-CR/CRi patients had an inferior outcome. Thus, one may conclude that for patients having received the less intensive decitabine induction, attainment of CR/CRi was not an absolute requirement for successful allografting. This interesting result is most likely multifactorial, for example, older patients not in CR/CRi after decitabine may better tolerate allografting and the post-transplant phase than non-CR patients having received repetitive cycles of standard, intensive chemotherapy.

In conclusion, this is the first large prospective study evaluating the potential predictive value of HbF as a biomarker for response to HMA treatment. The statistically significant association between HbF change from baseline to day 10 and CR/CRi indicates that HbF may indeed be a useful biomarker, warranting further research (particularly at later timepoints, i.e. after one or two cycles of HMA-based treatment). The role of baseline HbF is less clear but can also be addressed when serial determinations of HbF levels are being conducted, for instance in the ongoing DECIDER-2 phase III trial of decitabine and venetoclax +/− all-*trans* retinoic acid in newly diagnosed patients with AML.[20]

AUTHOR CONTRIBUTIONS

Julia Stomper: Conceptualization; investigation; writing – original draft. **Michal Kicinski:** Data curation; formal analysis; investigation; visualization; writing – review and editing. **Tobias Ma:** Data curation. **Thomas Meyer:** Data curation. **Sylvain Chantepie:** Resources. **Richard Noppeney:** Resources. **Mario Luppi:** Resources. **Ernesta Audisio:** Resources. **Laimonas Griškevičius:** Resources. **Andreas Neubauer:** Resources. **Robin Foà:** Resources. **Walter J. F. M. Van der Velden:** Resources. **Anna Candoni:** Resources. **Radovan Vrhovac:** Resources. **Gianluca Gaidano:** Resources. **Catharina Van Elssen:** Resources. **Mels Hoogendoorn:** Resources. **Maurizio Musso:** Resources. **Attilio Olivieri:** Resources. **Christian Junghanß:** Resources. **Emmanuel Bissé:** Methodology. **Stephanie Antunes:** Project administration. **Frédéric Baron:** Resources; funding acquisition. **Adriano Venditti:** Funding acquisition; resources. **Joop H. Jansen:** Conceptualization; resources; investigation; methodology. **Pierre W. Wijermans:** Conceptualization; resources. **Gerwin Huls:** Conceptualization; resources. **Michael Lübbert:** Conceptualization; funding acquisition; resources; methodology; investigation; writing – original draft; supervision.

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ACKNOWLEDGEMENTS

We are grateful to Johnson & Johnson for supporting this study. We wish to thank the patients and their families for participating in this study, providing their invaluable contribution. We also thank Thomas Epting, PhD, for continued support with HbF quantification. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

The AML21 trial was funded by Janssen Pharmaceuticals.

CONFLICT OF INTEREST STATEMENT

Michal Kicinski: Study funding paid to the institution from Astellas, BMS, Immunocore, Johnson & Johnson, MSD, Pierre Fabre. Mario Luppi: Advisory Board and meeting with honoraria: Abbvie, Jazz Pharma, Novartis, Grifols, Sanofi, Incyte, Istituto Gentili, Roche, Astrazeneca, Otsuka. Andreas Neubauer: José Carreras Leukemia foundation (AH 06/02). Anna Candoni: Consultancy for Pfizer, Gilead, Abbvie, Astellas, Servier, Amgen, Jazz, Incyte, Otsuka. Gianluca Gaidano: Research support from Gilead; Advisory Board and Speaker's Bureau for Abbvie, AstraZeneca, BeOne, Hikma, Incyte Johnson & Johnson and Lilly. Adriano Venditti has received research funding from Jazz Pharmaceuticals, Abbvie, Astrazeneca, Servier, Beigene; was a consultant for AbbVie, Amgen, Astellas Pharma, Astex Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Delbert Pharma, Glycostem, Janssen, Kite-Gilead, Menarini, Novartis, Otsuka, Pfizer, Servier, Istituto Gentili and Menarini-Stemline Therapeutics. Michael Lübbert: Honoraria: AbbVie, Astex, Janssen-Cilag, Otsuka, Syros; Research support: Cheplapharm (study drug), Johnson & Johnson / EORTC (research support to institution), German Research Foundation (SFB 992, C04). For the remaining authors, no relevant conflicts of interest were declared.

DATA AVAILABILITY STATEMENT

The data are available from the authors upon request.

ETHICS STATEMENT

The study was approved by the institutional review board of the University of Freiburg Medical Center.

PATIENT CONSENT

Written informed consent was obtained according to the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Stomper J, Kicinski M, Ma T, Meyer T, Chantepie S, Noppeney R, et al. Increase in fetal haemoglobin from baseline to day 10 is a biomarker for response to decitabine in AML: Results of the AML21 randomized phase III trial of the EORTC Leukemia Group, Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and German MDS Study Group. Br J Haematol. 2026;00:1–9. https://doi.org/10.1111/bjh.70874

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