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LETTER

Refinement of the prognostic impact of somatic *CEBPA* bZIP domain mutations in acute myeloid leukemia: Results of the AML Study Group (AMLSG)

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The transcription factor CCAAT/enhancer binding protein alpha (CEBPA) is a key regulator of myelopoiesis and granulocyte differentiation.[1,2] The intronless *CEBPA* gene on chromosome 19q13.1 encodes two DNA-binding protein isoforms: a full-length 42-kDa protein (p42) and a shorter 30-kDa isoform (p30), initiated from two distinct start sites.[2] The p42 isoform contains two N-terminal transactivation domains (TAD1, TAD2), whereas the p30 isoform lacks TAD1. Both isoforms contain the highly conserved C-terminal basic DNA-binding domain and the leucine zipper (bZIP) involved in DNA binding and protein dimerization. In younger adult patients, mutations of *CEBPA* (*CEBPA*^{mut}) are present in 5%–10% of newly diagnosed acute myeloid leukemia (AML); the frequency in older patients is considerably lower.[2–5] There are two mutational patterns: the first one clusters at the N-terminus involving the two TADs, typically frame-shift mutations; the second one at the C-terminus affecting bZIP, typically in-frame mutations. Out-of-frame TAD mutations result in the truncated p30 isoform that has been shown to act as a dominant negative of the p42 isoform and to be associated with increased proliferation and minimal differentiation of myeloid progenitors.[2,6] Depending on the position, in-frame bZIP mutations cause a p42 isoform defective either in DNA binding or homo- and heterodimerization.[3,7]

Approximately half of the *CEBPA*^{mut} AML exhibit biallelic mutations (*CEBPA*^{bi}), typically consisting of one TAD and one bZIP mutation on separate alleles.[3,4] Based on specific genetic features and its prognostic impact, *CEBPA*^{bi} was defined as a distinct entity within the 2016 WHO classification and was categorized as favorable in the risk stratification of the 2017 European LeukemiaNet (ELN) recommendations. Recent studies in pediatric and adult AML have demonstrated *CEBPA*^{bZIP}

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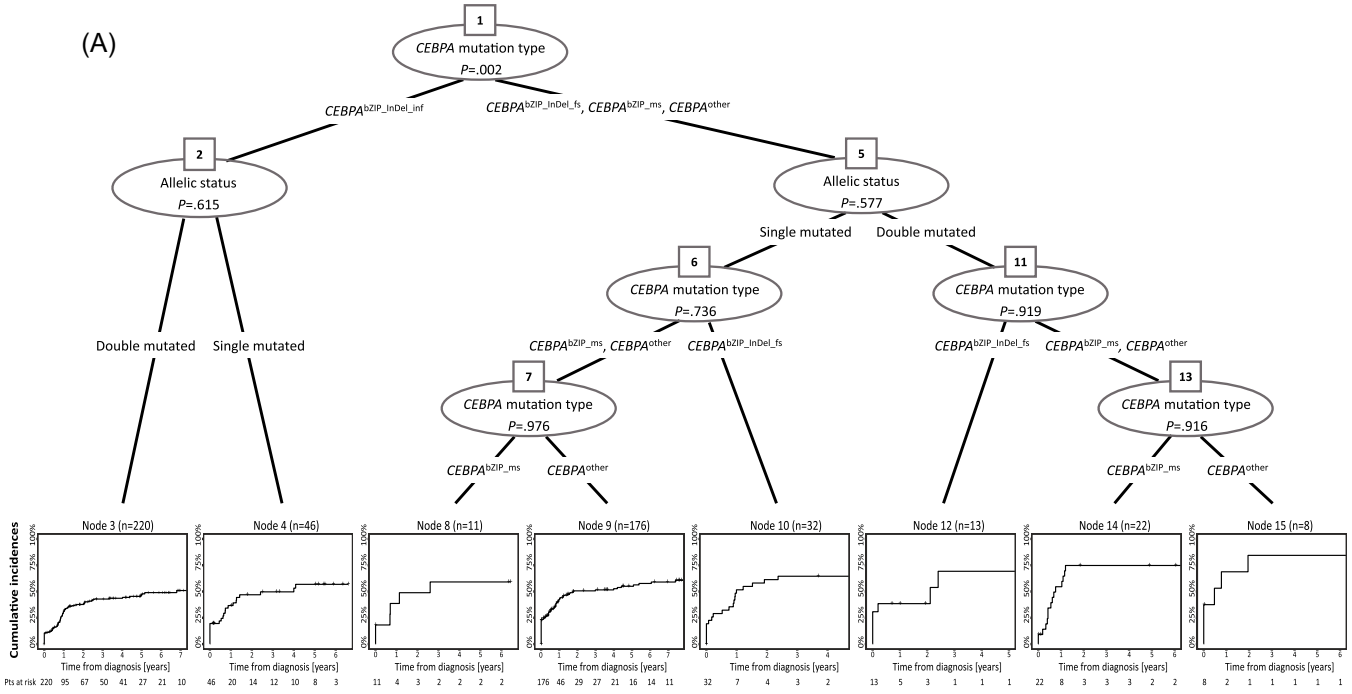
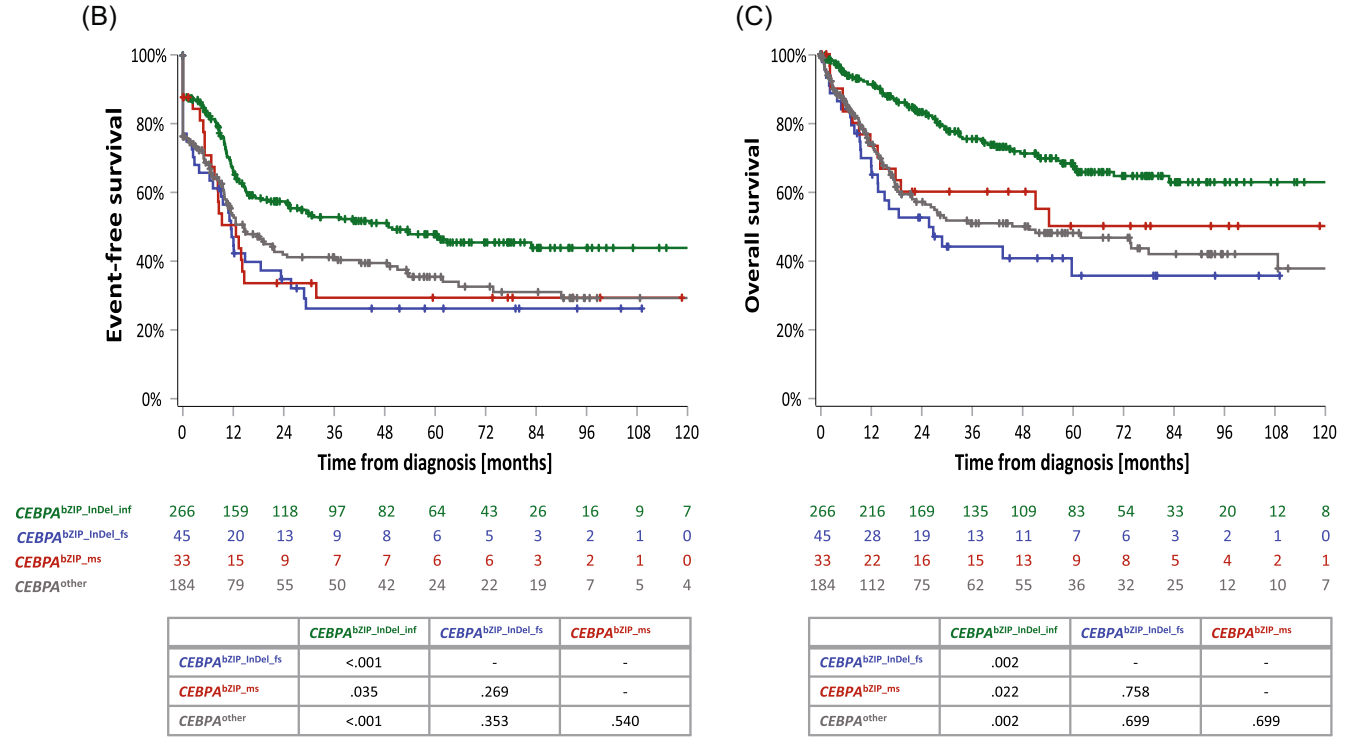
mutations, and in particular, in-frame mutations (*CEBPA*^{bZIP_inf}), to be associated with a unique gene-expression profile and favorable outcome, regardless of the mono- or biallelic status.[8–10] Based on these data, the former entity of AML with *CEBPA*^{bi} was expanded by single mutations in bZIP (smbZIP-*CEBPA*) in the current 2022 WHO classification and replaced by AML with *CEBPA*^{bZIP_inf} (irrespective of the allelic status) within the 2022 International Consensus Classification (ICC) of myeloid neoplasm and acute leukemias.[11,12] Furthermore, *CEBPA*^{bZIP_inf} (irrespective of the allelic status) is now categorized as favorable in the 2022 ELN risk stratification.[13]





	CEBPA^{bZIP_InDel_inf}	CEBPA^{bZIP_InDel_fs}	CEBPA^{bZIP_ms}
CEBPA^{bZIP_InDel_fs}	<.001	-	-
CEBPA^{bZIP_ms}	.035	.269	-
CEBPA^{other}	<.001	.353	.540

	CEBPA^{bZIP_InDel_inf}	CEBPA^{bZIP_InDel_fs}	CEBPA^{bZIP_ms}
CEBPA^{bZIP_InDel_fs}	.002	-	-
CEBPA^{bZIP_ms}	.022	.758	-
CEBPA^{other}	.002	.699	.699

FIGURE 1 Outcome of the 528 patients with *CEBPA*-mutated AML according to *CEBPA* genotypes. Conditional inference tree-structured event-free survival model for *CEBPA* mutation types with estimates of cumulative incidence of events (refractory disease, relapse, and/or death) in the terminal nodes. Hematopoietic-cell transplantation in first complete remission (HCT in CR1) was considered a competing event (A). Kaplan–Meier curves for event-free survival (B) and overall survival (C) according to *CEBPA* mutation types, irrespective of the allelic status. HCT in CR1 was not considered a competing event. Results of pairwise comparisons are provided below the *x*-axis.

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To evaluate the prognostic impact of *CEBPA*^{bZIP}, in particular to further characterize *CEBPA*^{bZIP_inf} mutations, we retrospectively analyzed 528 intensively treated adult *CEBPA*^{mut} AML patients (median age: 54 years, range: 18–82; ≤60 years: $n = 340$, >60 years: $n = 188$) enrolled in treatment trials of the German-Austrian AML Study Group (AMLSG) and/or entered into the AMLSG BiO Registry study (NCT01252485). *CEBPA* mutation status was evaluated centrally in two reference laboratories of the AMLSG; assays were harmonized and cross-validated between the two laboratories. Sequences were analyzed for type of *CEBPA* mutations (insertions/deletions either in-frame or frameshift, missense, and nonsense mutations), the precise localization of mutations (TAD1/2 and bZIP), and allelic status. Two hundred forty-three (46%) patients were enrolled in one of 12 AMLSG treatment trials (Supporting Information S1: Appendix) and 285 (54%) received intensive treatment according to the standard of care. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent for treatment and genetic testing was obtained from all patients.

Complete remission (CR), including CR with incomplete hematologic recovery during induction cycles 1 and 2, was achieved in 425/501 (85%) evaluable patients. Allogeneic hematopoietic-cell transplantation (HCT) in the first CR (CR1) was performed in 109 (21%) patients. The median follow-up time was 55.5 months (95% confidence interval [95% CI], 51.2–59.5). Median event-free survival (EFS) and median overall survival (OS) were 20.0 (95% CI: 14.4–30.6) and 172.4 months (95% CI: 72.5–NA), respectively. The 5-year EFS and OS rates were 42% and 55%, respectively. One hundred forty-one (26.7%) patients relapsed, and 195 (36.9%) died.

Of the 528 patients, 263 (49.8%) exhibited ≥2 *CEBPA* mutations (dm*CEBPA*), and 265 had monoallelic *CEBPA* mutations (sm*CEBPA*). To further refine *CEBPA* mutation types and to address their prognostic impact, patients were categorized into eight groups based on allelic status (dm*CEBPA* vs. sm*CEBPA*) and mutation type: (1) dm*CEBPA* with in-frame insertion/deletion in bZIP (dm*CEBPA*^{bZIP_InDel_inf}, $n = 220$), (2) frame-shift insertion/deletion or nonsense mutation in bZIP (dm*CEBPA*^{bZIP_InDel_fs}, $n = 13$), (3) missense mutation in bZIP (dm*CEBPA*^{bZIP_ms}, $n = 22$), (4) other (dm*CEBPA*^{other}, $n = 8$), (5) sm*CEBPA*^{bZIP_InDel_inf} ($n = 46$), (6) sm*CEBPA*^{bZIP_InDel_fs} ($n = 32$), (7) sm*CEBPA*^{bZIP_ms} ($n = 11$), or (8) sm*CEBPA*^{other} ($n = 176$). These eight groups differed significantly with regard to several clinical and concurrent genetic features as well as achievement of CR1 and outcome (Supporting Information S1: Table 1).

To evaluate the prognostic impact of the eight *CEBPA* mutation types, we performed conditional inference tree models for EFS and OS. Of the eight equally relevant groups, dm*CEBPA*^{bZIP_InDel_inf} and sm*CEBPA*^{bZIP_InDel_inf} patients separated from the other groups in the first tree based on significantly lower cumulative incidences of events (refractory disease, relapse, and/or death). No further partitioning was observed (Supporting Information S1: Figure 1). Assuming a prognostic impact primarily for mutation type rather than allelic status, subsequent conditional inference tree models were performed by splitting up *CEBPA* mutation types and allelic status for EFS and OS. In both the models, the *CEBPA*^{bZIP_InDel_inf} group again separated significantly from the other three groups in the first tree without further separation, confirming the significantly favorable prognosis, regardless of the allelic status (Figure 1A and Supporting Information S1: Figure 2).

Based on these findings, patients were subsequently categorized as *CEBPA*^{bZIP_InDel_inf} ($n = 266$), *CEBPA*^{bZIP_InDel_fs} ($n = 45$), *CEBPA*^{bZIP_ms} ($n = 33$), or *CEBPA*^{other} ($n = 184$), irrespective of the allelic status. These four groups differed significantly with regard to several clinical and concurrent genetic features as well as achievement of CR1. Most obviously, *CEBPA*^{bZIP_InDel_inf} patients were younger (median age in years: 49 vs. 66 vs. 60 vs 61; $p < .001$) and achieved a higher CR1 rate (91.4% vs. 81.8% vs. 83.3% vs. 76.2%; $p < .001$) (Supporting Information S1: Table 2). Irrespective of the allelic status, *CEBPA*^{bZIP_InDel_inf} patients had a significantly improved EFS (median [95% CI] 49.8 months [16.9–82.7] vs. 11.5 [8.3–14.6] for *CEBPA*^{bZIP_InDel_fs} vs. 12.6 [6.2–19.1] for *CEBPA*^{bZIP_ms} vs 14.6 [7.7–21.5] for *CEBPA*^{other}; $p < .001$) and OS (median [95% CI] NA for patients with *CEBPA*^{bZIP_InDel_inf} [NA–NA] vs. 25.7 months [10.2–41.3] for *CEBPA*^{bZIP_InDel_fs} vs. 54.3 [14.6–NA] for *CEBPA*^{bZIP_ms} vs. 45.5 [13.1–77.9] for *CEBPA*^{other}; $p < .001$) (Figure 1B,C). Of note, a sensitivity analysis in which survival times were censored at the date of HCT in CR1 revealed almost identical results (Supporting Information S1: Figure 3).

Multivariate Cox models for EFS and OS adjusted for sex, type of AML, *FLT3*-ITD, *NPM1* mutation status, white blood cell (WBC) count

TABLE 1 Multivariable analyses for outcome and response determining the prognostic significance of *CEBPA* mutation types.

	EFS		OS		CR	
	HR (95% CI)	*p*	HR (95% CI)	*p*	OR (95% CI)	*p*
Age (10-year increase)	1.18 (1.08–1.30)	<.001	1.48 (1.29–1.65)	<.001	0.84 (0.69–1.02)	.070
Female	1.11 (0.87–1.40)	.407	1.23 (0.92–1.64)	.171	1.53 (0.89–2.60)	.121
WBC (log10)	1.48 (1.18–1.84)	<.001	1.49 (1.15–1.95)	.003	0.79 (0.50–1.25)	.311
BM blasts	1.00 (0.99–1.01)	.926	1.00 (0.99–1.01)	.516	1.00 (0.99–1.01)	.887
De novo AML	1		1		1	
sAML	1.57 (1.00–2.46)	.052	1.31 (0.77–2.24)	.326	0.97 (0.37–2.53)	.943
tAML	0.61 (0.24–1.52)	.287	0.48 (0.17–1.34)	.163	2.36 (0.27–20.23)	.435
FLT3-ITD positive	1.22 (0.86–1.72)	.268	1.24 (0.83–1.87)	.292	0.75 (0.36–1.53)	.422
NPM1 mutation	0.61 (0.43–0.87)	.006	0.49 (0.33–0.75)	<.001	2.83 (1.33–6.03)	.007
CEBPA^{bZIP_InDel_inf}	1		1		1	
CEBPA^{bZIP_InDel_fs}	1.65 (1.08–2.54)	.022	2.29 (1.39–3.78)	.001	0.44 (0.17–1.12)	.084
CEBPA^{bZIP_ms}	1.67 (1.04–2.69)	.033	1.49 (0.83–2.66)	.185	0.55 (0.19–1.64)	.285
CEBPA^{other}	1.66 (1.19–2.31)	.003	2.29 (1.55–3.39)	<.001	0.24 (0.12–0.47)	<.001
HCT in CR1	0.38 (0.25–0.59)	<.001	0.50 (0.32–0.80)	.003	-	-

Abbreviations: 95% CI, 95% confidence interval; BM, bone marrow; CR, complete remission; EFS, event-free survival; ITD, internal tandem duplication; HCT in CR1, allogeneic hematopoietic cell transplantation in first CR; HR, hazard ratio; OS, overall survival; *p*, *p* value; sAML, secondary acute myeloid leukemia following myelodysplastic syndrome; tAML, therapy-related AML; WBC, white blood cell count.

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(log10 transformed), bone marrow blasts, and age including HCT in CR1 as a time-dependent variable (Supporting Information S1: Appendix) revealed increasing age and higher WBC as unfavorable factors, whereas *CEBPA*^{bZIP_InDel_inf}, *NPM1*^{mut}, and HCT in CR1 were favorable (Table 1).

A recent meta-analysis of 1010 adult *CEBPA*^{mut} AML from six different study groups characterized *CEBPA* mutational subgroups in more detail by evaluating their clinical and genetic features as well as their prognostic impact.[14] In line with our data, the authors showed that *CEBPA*^{bZIP_InDel_inf} mutations represent a subset of AML with distinct disease biology and clinical outcomes. Despite certain limitations, in particular, the retrospective nature spanning almost three decades with evolving different treatment approaches, both studies independently confirm the less favorable impact of in-frame bZIP missense mutations (currently subsumed in the category AML with *CEBPA*^{bZIP_inf} in the ICC and ELN risk classification). The less favorable impact of bZIP missense mutations might be explained by the finding that bZIP missense mutations localize differently and therefore have diverse functional consequences. *CEBPA*^{bZIP_InDel_inf} predominantly affects the fork region of bZIP, while *CEBPA*^{bZIP_ms} cluster in the basic region (Supporting Information S1: Figure 4). These different mutation patterns imply that *CEBPA*^{bZIP_ms} impair DNA binding, while *CEBPA*^{bZIP_InDel_inf} affects dimerization. Murine data have shown that missense mutations in the basic region of bZIP lead to a myeloproliferative disease transforming into overt AML,[7] while AML arises upon transplantation of transgenic cells carrying the most common in-frame insertion in bZIP (K313dup, K-allele) alone or in combination with an N-terminal mutation (L-allele), with the K/L combination driving the most aggressive AML.[15]

In this retrospective, exploratory analysis of 528 adult patients with newly diagnosed intensively treated patients with *CEBPA*^{mut} AML, we further refined the prognostic impact of different *CEBPA* mutation types, in particular, *CEBPA* mutations that are located in the bZIP domain. Our study shows that the beneficial effect is restricted to *CEBPA* bZIP InDel in-frame mutations, irrespective of the allelic status, whereas *CEBPA* bZIP missense mutations are associated with inferior outcomes. Our data as well as the data from Georgi et al. provide novel and clinically relevant results contributing to a further refinement of *CEBPA*^{mut} AML in the current ICC and WHO classifications as well as for risk stratification as recommended by the ELN.

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AUTHOR CONTRIBUTIONS

Frank G. Rücker, Andrea Corbacioglu, Hartmut Döhner, and Konstanze Döhner designed the study. Frank G. Rücker, Andrea Corbacioglu, Sibylle Cocciardi, Verena I. Gaidzik, Annika Meid, and Sophia Aicher performed experiments and validated data. Frank G. Rücker, Julia Krzykalla, Daniela Weber, and Axel Benner performed statistical analyses. Frank G. Rücker, Andrea Corbacioglu, Julia Krzykalla, Daniela Weber, Axel Benner, Hartmut Döhner, and Konstanze Döhner analyzed the results. Claudia Lengerke, Ulrich Germing, Gerald Wulf, Maisun A. Samra, Lino L. Teichmann, Michael Lübbert, Michael W. M. Kühn, Martin Bentz, Jörg Westermann, Lars Bullinger, Frank Stegelmann, Anika Schrade, Felicitas Thol, Michael Heuser, and Arnold Ganser collected and provided patient samples and clinical information. Frank G. Rücker, Andrea Corbacioglu, Hartmut Döhner, and Konstanze Döhner wrote the first draft of the manuscript; and all authors undertook manuscript writing, editing, and approval, revised the manuscript, and reviewed and approved the final version.

CONFLICT OF INTEREST STATEMENT

Frank G. Rücker reports honoraria from and consultancy for Jazz Pharmaceuticals, Novartis, and BMS/Celgene; travel support from Jazz Pharmaceuticals. Michael Lübbert reports an advisory role for Abbvie, Astex Pharmaceuticals, Imago BioSciences, Janssen, Otsuka, and Syros; research support from Janssen and Cheplapharm. Michael W. M. Kühn reports honoraria from and consultancy for Pfizer, Kura Oncology, Jazz Pharmaceuticals, BMS/Celgene, and Abbvie; speakers bureau of Gilead. Lars Bullinger reports honoraria from Abbvie, Amgen, Astellas, BMS/Celgene, Daiichi Sankyo, Gilead, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Pfizer, Roche, and Sanofi; research support from Bayer and Jazz Pharmaceuticals. Verena I. Gaidzik reports an advisory role for Jazz Pharmaceuticals, Abbvie, and Boehringer-Ingelheim; speakers bureau of Pfizer, Janssen, and Abbvie; and travel support from Abbvie. Frank Stegelmann reports honoraria from and consultancy for AOP Pharma, MorphoSys, BMS/Celgene, Incyte, Novartis, and Pfizer. Felicitas Thol reports an advisory role for Novartis, BMS, Abbvie, Menarini, and Rigel. Michael Heuser reports honoraria from Certara, Jazz Pharmaceuticals, Janssen, Novartis, and Sobi; paid consultancy for Abbvie, Amgen, BMS/Celgene, Glycostem, LabDelbert, Pfizer, PinotBio, and Servier; and research funding to his institution from Abbvie, Agios, Astellas, BMS/Celgene, Glycostem, Jazz Pharmaceuticals, Karyopharm, Loxo Oncology, and PinotBio. Hartmut Döhner declares being in an advisory role for Abbvie, Agios, Amgen, Astellas, AstraZeneca, Berlin Chemie, BMS/Celgene, Daiichi Sankyo, GEMoaB, Gilead, Janssen, Jazz Pharmaceuticals, Novartis, Servier, Stemline, and Syndax; research funding from Abbvie, Agios, Amgen, Astellas, BMS/Celgene, Jazz Pharmaceuticals, Kronos Bio, Novartis, and Pfizer. Konstanze Döhner reports an advisory role for Amgen, BMS/Celgene, Daiichi Sankyo, Janssen, Jazz Pharmaceuticals, Novartis, and Roche; research funding from Agios, Astex, Astellas, BMS/Celgene, and Novartis. All other authors declare no competing interest. The remaining authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. For original data, please contact Konstanze Döhner (konstanze.doehner@uniklinik-ulm.de). Individual participant data will not be shared.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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