**Supplemental Appendix**

**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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**PATIENTS AND METHODS**

**Patients and Treatment**

Fifty-hundred twenty-eight intensively treated *CEBPA*mut AML patients (median age 54 years, range: 18 to 82 years; ≤60 years: n=340, >60 years: n=188) entered into the AMLSG BiO Registry study (NCT01252485) were eligible for this retrospective analysis. Two-hundred forty-three patients were enrolled in one of twelve treatment trials of the German-Austrian AML Study Group (AMLSG): AML HD93 (n=11)1, AML HD98A (NCT00146120; n=45)2, AML HD98B (n=12)3, AMLSG 06-04 (NCT00151255; n=14)4, AMLSG 07-04 (NCT00151242; n=80)5, AMLSG 09-09 (NCT00893399; n=18)6, AMLSG 12-09 (NCT01180322; n=22)7, AMLSG 16-10 (NCT01477606; n=18)8, AMLSG 28-18 (NCT04027309; n=5), AMLSG 29-18 (NCT03839771; n=4), AMLSG 30-18 (NCT03897127; n=8), RATIFY (NCT00651261; n=6)9; the remaining 285 patients received intensive treatment according to standard of care.10 The study was conducted in accordance with the Declaration of Helsinki. Written informed consent for treatment and genetic testing was obtained from all patients.

**Molecular analyses**

Gene mutation analyses for *CEBPA, FLT3,* internal tandem duplication (ITD) and tyrosine kinase domain (TKD), as well as *NPM1* were performed as previously described.11-15 Additional mutational data on *GATA2*, *DNMT3A*, *TET2*, *ASXL1*, *RUNX1*, *WT1*, *IDH1/2* were available for subsets of patients.16-23

**Statistical analyses**

Complete remission (CR), CR with incomplete hematologic recovery (CRi), Event-free survival (EFS), and Overall survival (OS) were defined by standard criteria;24 responses included all CRs/CRis achieved during induction therapy. The primary endpoint EFS was calculated from the date of diagnosis to induction failure (ie, failure to achieve CR/CRi), relapse, or death, whichever occurred first. The secondary endpoint OS was calculated from the date of diagnosis to death of any cause. Patients not having experienced the event of interest at the end of follow-up are censored at the date of last contact. The median follow-up time was calculated using the reverse Kaplan-Meier estimate.25 The impact of *CEBPA* mutation types on EFS and OS was evaluated using conditional inference tree models.26 In the first model for the primary endpoint EFS, *CEBPA* mutation types defining eight distinct groups, were selected as variables. For subsequent models on EFS and OS, the variables were split up according to (i) mutation type and (ii) allelic status. To address the impact of allogeneic hematopoietic-cell transplantation (HCT) in first CR (CR1) in the models for EFS and OS, HCT in CR1 was considered as competing event. Distributions of cumulative incidences were estimated by the method of Aalen and Johansen. Logistic regression and Cox proportional hazards regression models were used to analyze the effect of *CEBPA* mutation types on CR (including CRi), EFS, and OS, adjusted for sex, type of AML, *FLT3*-ITD, and *NPM1* mutation status as dichotomous variables, as well as white blood cell (WBC) count (log10 transformed), bone marrow (BM) blasts and age as continuous variables. In the Cox regression models, HCT in CR1 was included as a time-dependent variable. Missing values of the covariates were addressed via multiple imputation by chained equations. The Kruskal-Wallis test was used for comparing quantitative variables between patient subgroups according to *CEBPA* genotypes; categorical variables were compared by means of Fisher’s exact test. Survival distributions were estimated using the Kaplan-Meier method, and differences between groups were analyzed by log-rank tests. An effect was considered significant if its *P*-value was less than 5%. The analyses were not adjusted for multiple testing. All statistical analyses were performed with IBM SPSS Statistics 28 and/or the statistical software environment R, version 4.1.3, using the R packages survival, version 3.2-13, and party, version 1.3-11.

**REFERENCES**

1. Schlenk RF, Benner A, Hartmann F, et al.; AML Study Group Ulm (AMLSG ULM). Risk-adapted postremission therapy in acute myeloid leukemia: results of the German multicenter AML HD93 treatment trial. Leukemia. 2003;17(8):1521-1528.
2. Schlenk RF, Döhner K, Mack S, et al. Prospective evaluation of allogeneic hematopoietic stem-cell transplantation from matched related and matched unrelated donors in younger adults with high-risk acute myeloid leukemia: German-Austrian trial AMLHD98A. J Clin Oncol. 2010;28(30):4642-4648.
3. Schlenk RF, Fröhling S, Hartmann F, et al. Intensive consolidation versus oral maintenance therapy in patients 61 years or older with acute myeloid leukemia in first remission: results of second randomization of the AML HD98-B treatment Trial. Leukemia. 2006;20(4):748-750.
4. Tassara M, Döhner K, Brossart P, et al. Valproic acid in combination with all-trans retinoic acid and intensive therapy for acute myeloid leukemia in older patients. Blood. 2014;123(26):4027-4036.
5. Schlenk RF, Lübbert M, Benner A, et al.; German-Austrian Acute Myeloid Leukemia Study Group. All-trans retinoic acid as adjunct to intensive treatment in younger adult patients with acute myeloid leukemia: results of the randomized AMLSG 07-04 study. Ann Hematol. 2016;95(12):1931-1942.
6. Schlenk RF, Paschka P, Krzykalla J, et al. Gemtuzumab Ozogamicin in NPM1-Mutated Acute Myeloid Leukemia: Early Results From the Prospective Randomized AMLSG 09-09 Phase III Study. J Clin Oncol. 2020;38(6):623-632.
7. Schlenk RF, Weber D, Herr W, et al. Randomized phase-II trial evaluating induction therapy with idarubicin and etoposide plus sequential or concurrent azacitidine and maintenance therapy with azacitidine. Leukemia. 2019;33(8):1923-1933.
8. Döhner H, Weber D, Krzykalla J, et al. Midostaurin plus intensive chemotherapy for younger and older Patients with AML and FLT3 internal tandem duplications. Blood Adv. 2022;6(18):5345-5355.
9. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017;377(5):454-464.
10. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
11. Fröhling S, Schlenk RF, Stolze I, et al. CEBPA mutations in younger adults with acute myeloid leukemia and normal cytogenetics: prognostic relevance and analysis of cooperating mutations. J Clin Oncol. 2004;22(4):624-633.
12. Wouters BJ, Löwenberg B, Erpelinck-Verschueren CA, van Putten WL, Valk PJ, Delwel R. Double CEBPA mutations, but not single CEBPA mutations, define a subgroup of acute myeloid leukemia with a distinctive gene expression profile that is uniquely associated with a favorable outcome. Blood. 2009;113(13):3088-3091.
13. Taskesen E, Bullinger L, Corbacioglu A, et al. Prognostic impact, concurrent genetic mutations, and gene expression features of AML with CEBPA mutations in a cohort of 1182 cytogenetically normal AML patients: further evidence for CEBPA double mutant AML as a distinctive disease entity. Blood. 2011;117(8):2469-2475.
14. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017;377(5):454-464.
15. Schlenk RF, Döhner K, Krauter J, et al.; German-Austrian Acute Myeloid Leukemia Study Group. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med. 2008;358(18):1909-1918.
16. Theis F, Corbacioglu A, Gaidzik VI, et al. Clinical impact of GATA2 mutations in acute myeloid leukemia patients harboring CEBPA mutations: a study of the AML study group. Leukemia. 2016;30(11):2248-2250.
17. Gaidzik VI, Schlenk RF, Paschka P, et al. Clinical impact of DNMT3A mutations in younger adult patients with acute myeloid leukemia: results of the AML Study Group (AMLSG). Blood. 2013;121(23):4769-4777.
18. Gaidzik VI, Paschka P, Späth D, et al. TET2 mutations in acute myeloid leukemia (AML): results from a comprehensive genetic and clinical analysis of the AML study group. J Clin Oncol. 2012;30(12):1350-1357.
19. Paschka P, Schlenk RF, Gaidzik VI, et al. ASXL1 mutations in younger adult patients with acute myeloid leukemia: a study by the German-Austrian Acute Myeloid Leukemia Study Group. Haematologica. 2015;100(3):324-330.
20. Gaidzik VI, Bullinger L, Schlenk RF, et al. RUNX1 mutations in acute myeloid leukemia: results from a comprehensive genetic and clinical analysis from the AML study group. J Clin Oncol. 2011;29(10):1364-1372.
21. Gaidzik VI, Schlenk RF, Moschny S, et al.; German-Austrian AML Study Group. Prognostic impact of WT1 mutations in cytogenetically normal acute myeloid leukemia: a study of the German-Austrian AML Study Group. Blood. 2009;113(19):4505-4511.
22. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol. 2010;28(22):3636-3643.
23. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. N Engl J Med. 2016;374(23):2209-2221.
24. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
25. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17(4):343-346.
26. Hothorn T, Hornik K, Zeileis A. (2006) Unbiased Recursive Partitioning: A Conditional Inference Framework, Journal of Computational and Graphical Statistics. 2006;15(3):651-674.

**SUPPLEMENTAL FIGURE LEGENDS**

**Supplemental Figure 1.** Conditional inference tree-structured event-free survival model for *CEBPA* mutation types with estimates of cumulative incidences of events (refractory disease, relapse, and/or death) in the terminal nodes. Type of *CEBPA* mutation and allelic status were split up into two variables. Hematopoietic-cell transplantation in first complete remission was considered as competing event.

**Supplemental Figure 2.** Conditional inference tree-structured overall survival model for *CEBPA* mutation types with cumulative incidences in the terminal nodes. Type of *CEBPA* mutation and allelic status were split up into two variables. Hematopoietic-cell transplantation in first complete remission was considered as competing event.

**Supplemental Figure 3.** Kaplan-Meier curves of sensitivity analysis for Event-free survival (A) and Overall survival (B) according to *CEBPA* mutation types, irrespective of the allelic status. Survival times were censored at date of hematopoietic-cell transplantation in first complete remission. Results of pairwise comparisons are provided below the x-axis.

**Supplemental Figure 4.** Distribution of *CEBPA* bZIP in-frame mutations according to mutation type.

**Supplemental Table 1:** Patient and disease characteristics according to *CEBPA* genotypes

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **dm*CEBPA***  **bZIPInDel-inf**  **(n=220)** | **dm*CEBPA***  **bZIPInDel-fs**  **(n=13)** | **dm*CEBPA***  **bZIPms**  **(n=22)** | **dm*CEBPA***  **other**  **(n=8)** | **sm*CEBPA***  **bZIPInDel-inf**  **(n=46)** | **sm*CEBPA***  **bZIPInDel-fs**  **(n=32)** | **sm*CEBPA***  **bZIPms**  **(n=11)** | **sm*CEBPA***  **other**  **(n=176)** | ***P* value** |
| Age in years, median (range) | 48 (18-82) | 67 (21-76) | 62 (35-79) | 68 (21-78) | 55 (26-75) | 62 (29-77) | 52 (28-74) | 61 (18-81) | <.001 |
| Gender, n (%)  Female  Male | 99 (45)  121 (55) | 5 (38)  8 (62) | 10 (45)  12 (55) | 3 (37)  5 (63) | 21 (46)  25 (53) | 16 (50)  16 (50) | 2 (18)  9 (82) | 88 (50)  88 (50) | .614 |
| AML type, n (%)  de novo  sAML  tAML  unknown | 202 (99)  2 (1)  1 (0)  15 | 9 (75)  1 (8)  2 (17)  1 | 20 (100)  0  0  2 | 6 (86)  0  1 (14)  1 | 36 (88)  3 (7)  2 (5)  5 | 22 (76)  7 (24)  0  3 | 10 (100)  0  0  1 | 140 (85)  19 (12)  5 (3)  12 | <.001 |
| Laboratory, median (range)  WBC in G/l  Hb in g/dl  Platelets in G/l  LDH in U/l  BM blasts in %  PB blasts in % | 26.6 (2.2-469.0)  10.1 (3.5-15.4)  36 (4-287)  454 (133-2795)  75 (2-100)  74 (0-100) | 8.8 (1.4-356.7)  7.5 (4.5-12.9)  56 (14-141)  370 (227-1327)  50 (40-82)  32 (5-86) | 14.4 (1.5-156.6)  9.9 (6.1-12.6)  42 (7-154)  422 (184-1923)  72 (35-89)  61 (0-86) | 37.2 (4.9-345.0)  9.2 (8.6-11.6)  72 (64-139)  506 (295-2295)  64 (40-85)  58 (19-100) | 23.3 (1.2-403.5)  9.6 (6.0-11.4)  54 (12-307)  353 (124-3452)  80 (20-100)  66 (0-98) | 26.3 (1.2-328.0)  8.8 (5.3-13.2)  61 (22-2461)  358 (65-3236)  78 (0-100)  46 (1-99) | 18.3 (0.1-102.9)  8.6 (5.1-11.5)  57 (9-361)  443 (218-1011)  82 (9-99)  62 (0-96) | 15.9 (0.8-333.8)  9.4 (2.7-13.9)  50 (2-310)  410 (119-6023)  79 (0-100)  44 (0-98) | .142  .002  <.001  .631  .255  <.001 |
| Cytogenetics, n (%)  Normal karyotype  Abnormal karyotype  unknown | 161 (77)  49 (23)  10 | 9 (75)  3 (25)  1 | 12 (57)  9 (43)  1 | 6 (75)  2 (25)  0 | 28 (65)  15 (35)  3 | 25 (86)  4 (14)  3 | 9 (90)  1 (10)  1 | 129 (77)  38 (23)  9 | .203 |
| Treatment, n (%)  Primary alloHCT  Salvage alloHCT | 51 (23)  58 (26) | 2 (15)  3 (23) | 1 (5)  7 (32) | 0  1 (13) | 9 (20)  12 (26) | 8 (25)  4 (13) | 2 (18)  3 (27) | 41 (23)  29 (16) | .397  .220 |
| Co-mutations, n/total n (%)  *FLT3*-ITD  High allelic ratio (>0.5)  *FLT3*-TKD  *NPM1*  *GATA2*  *DNMT3A*  *TET2*  *ASXL1*  *RUNX1*  *WT1*  *IDH1*  *IDH2* | 18/220 (8)  3/18 (17)  5/220 (2)  0/220 (0)  23/77 (30)  2/85 (2)  6/73 (8)  1/89 (1)  1/102 (1)  18/73 (25)  2/147 (1)  3/147 (2) | 1/13 (8)  0/1 (0)  1/13 (8)  0/13 (0)  0/2 (0)  0/0 (0)  0/0 (0)  2/5 (40)  1/5 (20)  0/0 (0)  1/7 (14)  3/7 (43) | 0/22 (0)  0/0 (0)  0/22 (0)  0/22 (0)  2/8 (25)  0/9 (0)  0/4 (0)  3/11 (27)  0/14 (0)  1/4 (25)  2/17 (12)  1/17 (6) | 4/8 (50)  2/4 (50)  0/8 (0)  2/8 (25)  0/4 (0)  2/4 (50)  0/1 (0)  0/3 (0)  1/5 (20)  0/2 (0)  0/5 (0)  1/5 (20) | 5/46 (11)  3/5 (60)  0/46 (0)  4/46 (9)  3/22 (14)  3/16 (19)  1/14 (7)  1/27 (4)  4/30 (13)  2/13 (15)  2/34 (6)  2/34 (6) | 10/32 (31)  3/10 (30)  2/32 (6)  10/32 (31)  2/10 (20)  6/10 (60)  2/5 (40)  1/10 (10)  4/11 (36)  0/6 (0)  0/20 (0)  5/20 (25) | 2/11 (18)  2/2 (100)  1/11 (9)  1/11 (9)  0/7 (0)  2/7 (29)  2/6 (33)  0/8 (0)  1/8 (13)  0/6 (0)  0/9 (0)  2/9 (22) | 63/176 (36)  36/63 (57)  5/176 (3)  86/176 (49)  3/50 (6)  20/59 (34)  7/30 (23)  6/60 (10)  5/63 (8)  4/34 (12)  6/101 (6)  15/101 (15) | <.001  .031  .443  <.001  .031  <.001  .105  .001  <.001  .388  .167  <.001 |
| Response and Outcome  CR1, n/total n (%)  Median EFS, months  Median OS, months | 196/212 (93.0)  53.5  NR | 10/13 (76.9)  25.7  NR | 17/20 (85.0)  9.3  54.2 | 4/7 (57.1)  5.8  10.9 | 37/43 (86.0)  48.7  NR | 26/31 (83.9)  11.5  16.2 | 8/10 (80.0)  31.7  NR | 127/165 (77.0)  14.6  73.4 | .002  .004  <.001 |

Abbreviations: sAML, secondary acute myeloid leukemia following myelodysplastic syndrome; tAML, therapy-related AML; WBC, white blood cell count; Hb, hemoglobin; LDH, lactate dehydrogenase; BM, bone marrow; PB, peripheral blood; Primary alloHCT, allogeneic hematopoietic cell transplantation in first complete remission; ITD, internal tandem duplication; TKD, tyrosine kinase domain; CR1, first complete remission.

**Supplemental Table 2:** Patient and disease characteristics according to *CEBPA* mutation type, irrespective of allelic status

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | ***CEBPA*bZIP\_InDel-inf**  **(n=266)** | ***CEBPA*bZIP\_InDel\_fs**  **(n=45)** | ***CEBPA*bZIP\_ms**  **(n=33)** | ***CEBPA*other**  **(n=184)** | ***P* value** |
| Age in years, median (range) | 49 (18-82) | 66 (21-82) | 60 (28-79) | 61 (18-81) | <.001 |
| Gender, n (%)  Female  Male | 120 (45)  146 (55) | 21 (47)  24 (53) | 12 (36)  21 (64) | 91 (50)  93 (50) | .532 |
| AML type, n (%)  de novo  sAML  tAML  unknown | 238 (97)  5 (2)  3 (1)  20 | 31 (76)  8 (19)  2 (5)  4 | 30 (100)  0 (0)  0 (0)  3 | 146 (85)  19 (11)  6 (4)  13 | <.001 |
| Laboratory, median (range)  WBC in G/l  Hb in g/dl  Platelets in G/l  LDH in U/l  BM blasts in %  PB blasts in % | 26.0 (1.2-469.0)  10.0 (3.5-15.4)  37 (4-307)  409 (124-3452)  75 (2-100)  74 (0-100) | 19.1 (1.2-356.7)  8.6 (4.5-13.2)  60 (14-241)  365 (65-3236)  60 (0-100)  43 (1-99) | 14.4 (0.1-156.6)  9.7 (5.1-12.6)  50 (7-361)  429 (184-1923)  75 (9-99)  62 (0-96) | 16.0 (0.8-345.0)  9.3 (2.7-13.9)  52 (2-310)  412 (119-6023)  79 (0-100)  44 (0-100) | .125  <.001  <.001  .795  .478  <.001 |
| Cytogenetics, n (%)  Normal karyotype  Abnormal karyotype  unknown | 189 (75)  64 (25)  13 | 34 (83)  7 (17)  4 | 21 (68)  10 (32)  2 | 135 (77)  40 (23)  9 | .463 |
| Treatment, n (%)  Primary alloHCT  Salvage alloHCT | 60 (23)  49 (18) | 10 (22)  6 (13) | 3 (9)  6 (18) | 41 (22)  26 (14) | .354  .602 |
| Co-mutations, n/total n (%)  *FLT3*-ITD  High allelic ratio (>0.5)  *FLT3*-TKD  *NPM1*  *GATA2*  *DNMT3A*  *TET2*  *ASXL1*  *RUNX1*  *WT1*  *IDH1*  *IDH2* | 23/266 (9)  6/23 (26)  5/266 (2)  4/266 (2)  27/108 (25)  5/101 (5)  7/87 (8)  2/116 (2)  5/132 (4)  20/86 (23)  4/181 (2)  5/181 (3) | 11/45 (24)  3/11 (27)  3/45 (7)  10/45 (22)  3/14 (21)  6/10 (60)  2/5 (40)  3/15 (20)  5/16 (31)  0/6 (0)  1/27 (4)  8/27 (30) | 2/33 (6)  2/2 (100)  1/33 (3)  1/33 (3)  2/17 (12)  2/16 (13)  2/10 (20)  3/19 (16)  1/22 (5)  1/10 (10)  2/26 (8)  3/26 (12) | 67/184 (36)  38/67 (57)  5/184 (3)  88/184 (48)  4/60 (7)  22/63 (35)  7/31 (23)  6/63 (10)  6/68 (9)  4/36 (11)  6/106 (6)  16/106 (15) | <.001  .015  .328  <.001  .025  <.001  .051  .006  <.001  .213  .346  <.001 |
| Response  CR1, n/total n (%) | 233/255 (91.4) | 36/44 (81.8) | 25/30 (83.3) | 131/172 (76.2) | <.001 |

Abbreviations: sAML, secondary acute myeloid leukemia following myelodysplastic syndrome; tAML, therapy-related AML; WBC, white blood cell count; Hb, hemoglobin; LDH, lactate dehydrogenase; BM, bone marrow; PB, peripheral blood; Primary alloHCT, allogeneic hematopoietic cell transplantation in first complete remission; ITD, internal tandem duplication; TKD, tyrosine kinase domain; CR1, first complete remission.