



## Validation of mutated CEBPA bZIP as a distinct prognosis entity in acute myeloid leukemia: a study by the Spanish PETHEMA registry

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## Validation of mutated *CEBPA* bZIP as a distinct prognosis entity in acute myeloid leukemia: a study by the Spanish PETHEMA registry

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**RUNNING HEAD:** Real-life validation of *CEBPA* bZIP-in frame AML

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The prognosis for patients diagnosed with acute myeloid leukemia (AML) suitable for intensive chemotherapy, is defined by the presence of specific genetic abnormalities (1, 2). Among these, mutations in CCAAT/enhancer binding protein alpha (*CEBPA*) gene have classically classified as favorable risk(3). The frequency of *CEBPA* gene mutations ranges 7-20%(4, 5), being present mostly in cytogenetically normal patients. While wild-type *CEBPA* (*CEBPAwt*) or *CEBPA* single mutation (*CEBPAsm*) patients have ~60% risk of relapse, this risk is ~40% in those with *CEBPA double mutation* (*CEBPAdm*)(5). These findings led to the inclusion of *CEBPAdm* AML as a distinct diagnostic entity in the 2016 WHO Classification(6) and as favorable risk group by 2017 European Leukemia Net (ELN) risk classification(7). However, a study in children and young adults enrolled in Children's Oncology Group Trials showed that *CEBPA mutations in bZIP region* conferred favorable prognosis, regardless of whether they are *CEBPAsm* or *CEBPAdm*(8). This finding was confirmed in adult patients enrolled in protocols of the Study Alliance Leukemia(9), where bZIP mutations were associated with higher overall survival (OS) and complete remission (CR) rate. This data led to refinement of 2022 ELN risk classification(2), defining as favorable risk only the presence of inframe bZIP *CEBPA* mutation (*CEBPA-bZIP-inf*).

In this study, we aim to describe the incidence, clinical-biological features, and prognosis of *CEBPA* mutations, including *CEBPA-bZIP-inf*, in a large series of real-life consecutive patients, homogeneously studied with harmonized Next Generation Sequencing (NGS) methodologies. For this purpose, we conducted a retrospective, non-interventional, multicenter study in the PETHEMA epidemiologic registry (N=2434 consecutive patients with available centralized NGS) involving seven Spanish central-core laboratories (PLATAFO-LMA protocol, NCT04446741). The consortium members are included in **Supplementary material**.

Of them, a total of 696 Intensively Treated AML (IT AML) patients ( $\geq 18$  years) diagnosed with AML according to WHO 2016(6) criteria since October 2017, with treatment and survival data were included. The ELN2017 was used for risk stratification(7). The intensive schedules consisted mainly in anthracycline plus Ara-C-based regimens, such as 3+7 (idarubicin or daunorubicin and Ara-C) (n=493, 66.5%), mitoxantrone plus Ara-C, FLAG-IDA, FLAT (fludarabine, Ara-C, and topotecan), or ICE (idarubicin, Ara-C, and etoposide).

Genomic DNA, extracted from bone marrow (or peripheral blood) of each patient at the time of diagnosis, was shipped and analyzed at reference hospitals. The AML PETHEMA Diagnostic network employs harmonized next-generation sequencing

protocols for analysis and reporting with external quality control rounds(10). All reference laboratories performed the analysis of at least 32 genes established by consensus due to their importance in AML. In all cases, *CEBPA* gene was entirely sequenced(10). Mutation in bZIP-inf was considered if they are multiples of 3bp and affect DNA binding, fork or bZIP from amino acid position 278 to C-terminus as previously stated(9).

A total of 82 patients out of 696 IT AML patients (11.8%) harbored *CEBPA* gene mutations by NGS. Among them, 45 had mutation within bZIP domain and 40 fulfilled criteria of *CEBPA*-bZIP-inf (5.7%). Among *CEBPA*-bZIP-inf, 22 were *CEBPAdm* and 18 *CEBPAsm*. **Figure 1S** shows patients flow chart classified from the detection of any *CEBPA* gene mutation to the final categorization as *CEBPA*-bZIP-inf.

Main characteristics of entire cohort according to *CEBPA* status [i.e, bZIP-inf vs. other *CEBPA* mutations (*CEBPA* other mut) vs. wild-type *CEBPA* (*CEBPAwt*)] are detailed in **Table 1**. Patients with *CEBPA*-bZIP-inf were significantly younger than other *CEBPAmut* and *CEBPAwt* (49.6 vs. 60.6 vs. 57.8 years respectively,  $P=0.009$ ). Patients harboring *CEBPA*-bZIP-inf mutation had an estimated 3-year survival of 83.3% (95%CI, 58.3-100) better than those with *CEBPA* other mut (54.3%, 95%CI 34.9-84.4) and those with *CEBPAwt* (47.2%, 95%CI 41.5-53.7) albeit no statistical differences were reached ( $P=0.17$  for both comparisons) (**Figure 1A**). To seek the prognosis importance of being strictly “inframe” bZIP mutations, we performed similar OS analyses grouping all bZIP mutations (including not-inframe). Thus, patients harboring grouped *CEBPA*-bZIP mutations had also a 3-year survival [87.5 (95% CI, 67.3-100)] better than those with *CEBPA* other mut [47.9 (95%CI, 27.9-82.2)] and those with *CEBPAwt* [47.2% (95%CI (41.5-53.7),  $P=0.068$  for both comparisons)] (**Figure 1B**).

The mutational landscape found in patients with bZIP-inf (median number of mutations 1.5, range 0-5) compared *CEBPA* other mut (median number of mutations 2.5, range 0-7) is displayed in **Figure 2A**. We identified at least one mutation in any of the genes included in the study panel in 82 patients with *CEBPA* mutations (median. Only 17 patients (13.69%) had no additional mutations. From these 17 patients (47 % *CEBPA*-bZIP-inf), karyotype data was only available for 5 patients (2 patients had intermediate risk, 1 had favorable risk and 2 had normal karyotype). We identified significantly higher percentage of mutations in *WT1*, *GATA2* y *C-KIT* in patients with *CEBPA*-bZIP-inf compared to *CEBPA* other mut (20% vs 4.8%, 20% vs. 7.1 and 5% vs. 0%, respectively). By contrast, *CEBPA* other mut patients harbored significantly higher percentage of mutations in *ASXL1* and *NPM1* genes than *CEBPA*-bZIP-inf (19% vs.

2.5%, 28.5% vs. 2.5%, and 14.3% vs. 5% respectively). These differences are maintained when grouping all *CEBPA*-bZIP mutations compared to *CEBPA* other mut.

Additionally, we performed analysis to infer the timing of co-mutation occurrence among all *CEBPA* mutated AML patients by using the Bradley-Terry model(11). As displayed in **Figure 2B**, *TP53* mutations, chromatin modifiers mutations (*ASXL1*, *EZH2*), epigenetic regulators (*TET2*, *DNMT3A*) and splicing machinery mutations (*SF3B1*, *UAF1*) seem to occur earlier. By contrast, mutations in *NPM1* and signaling pathways (*NRAS*, *KRAS* and *FLT3*) seem to occur later.

Finally, we studied the impact on OS of the presence of co-mutations in *CEBPA*-bZIP-inf and *CEBPA* other mut. The presence of mutations in *WT1* and *GATA2* genes did not modify the prognosis of *CEBPA*-bZIP-inf patients. In the same way, no statistical differences were found analyzing the impact of mutations in the myelodysplasia-associated genes *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, *RUNX1* or *STAG2* in patients with *CEBPA*-bZIP-inf. However, the presence of mutations in *TET2* genes conferred worse outcomes to *CEBPA*-bZIP-inf ( $P=0.064$ ) and *FLT3* mutations conferred significant worse outcomes only to *CEBPA* other mut patients ( $P=0.042$ ). These differences are maintained when grouping all *CEBPA*-bZIP mutations compared to *CEBPA* other mut.

Since the first description of mutations in *CEBPA* gene in AML, the definition of which type had diagnosis entity and clinical prognostic impact, has evolved(3). Currently, WHO 2022 includes biallelic *CEBPA* mutations (independent of the gene region) and single mutations located in the bZIP region(12), but ICC only accepts a narrower definition *CEBPA*-bZIP-inf mutations (independent of the allelic state)(13) as defined also as favorable prognosis category in ELN 2022(2). Therefore, this recent step forward of ICC and ELN2002 statements implies a meaningful paradigm shift in the way AML with *CEBPA* mutations must be diagnosed and prognostically defined. This notable change has been made based mainly on the results of two large series of pediatric and adult patients intensively treated in clinical protocols and analyzed using different methodologies(8, 9).

We confirm that *CEBPA*-bZIP-inf is associated with favorable prognosis among fit AML patients intensively treated, but we also suggest that all *CEBPA*-bZIP (inframe and others) could be categorized as favorable risk. These findings were also in agreement with those reported by Taube et al when analyzed only bZIP-inf and all bZIP mutations differentially(9). Importantly, other studies have reported favorable outcomes when

grouping all bZIP mutations(8, 14). Altogether, these results question whether the restriction to bZIP-inf mutations as defined by ICC and ELN2022 has a meaningful clinical or diagnostic impact, while it is sure that it could increase complexity when reporting and interpreting these mutations. Moreover, although some data suggest that *CEBPA* bZIP-mutant does not downregulate miR-182 and this incapability could be restricted to typical in-frame bZIP mutations(15), there is no a clear evidence of *CEBPA*-bZIP-inf as a biological distinct entity.

Additionally, we observed that *CEBPA*-bZIP-inf carried more frequently well-known co-mutations as *WT1* and *GATA2*, whereas in *CEBPA* other mut, *ASXL1* mutations and *NPM1* mutations were more frequent. It is important to remark the relatively frequent co-existence of mutations in *NPM1* and *CEBPA*, both defining diagnostic entities in current WHO and ICC classifications , which is homogeneously found in up to 5% of *CEBPA*-bZIP-inf cases in our series and others(8, 9, 14). This finding opens the question of the real-independent diagnosis entity of *CEBPA*-bZIP-inf which should be mutually exclusive with other genetically defined AML entities.

The role of co-mutations in *CEBPA* mutated patients has been extensively analyzed with discordant results. Prior studies reported inferior outcomes among *CEBPAdm* with *GATA* or *WT1* co-mutations(3, 5) However, when restricting the analyses to the bZIP-inf, the negative impact of these co-mutations is less clear since conflicting results have been published(8, 9, 14). In our series, neither *GATA* nor *WT1* mutations adversely impact clinical outcome. Interestingly, the presence of mutations in *TET2* gene could negatively impact prognosis in *CEBPA*-bZIP-inf patients in agreement with Taube et al(9).

The strengths of our study are to be a very large series of real-life consecutive patients, homogeneously analyzed within a harmonized NGS nationwide platform. In summary, *CEBPA*-bZIP-inf confer a favorable OS, compared to *CEBPA* other mut, but the narrow definition of in-frame could not be clinically relevant while increasing complexity for routine practice. although larger series are undoubtedly needed to firmly conclude this statement.



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**Table 1.** Demographic and clinical characteristics of intensively treated AML patients including wild-type *CEBPA*, bZIP in-frame *CEBPA* mutation and other *CEBPA* mutation.

	Total	<i>CEBPA</i> bZIPinf	<i>CEBPA</i> other mut	<i>CEBPA</i> wt	P-value
<i>n</i>	696	40	42	614	
Sex, <i>n</i> (%)					0.10
Female	310 (44.5%)	12 (30.0%)	16 (38.1%)	282 (45.9%)	
Male	386 (55.5%)	28 (70.0%)	26 (61.9%)	332 (54.1%)	
Age, median (IQR)	57.5 (48.0 - 64.7)	49.6 (39.6 - 58.3)	60.6 (47.9- 66.6)	57.8 (48.2 - 64.8)	0.009
Age group, <i>n</i> (%)					< 0.001
> 60	288 (41.4%)	6 (15.0%)	23 (54.8%)	259 (42.2%)	
< 60	408 (58.6%)	34 (85.0%)	19 (45.2%)	355 (57.8%)	
Type of AML, <i>n</i> (%)					0.19
De-novo	449 (73.5%)	19 (90.5%)	18 (75.0%)	412 (72.8%)	
Secondary	162 (26.5%)	2 (9.5%)	6 (25.0%)	154 (27.2%)	
ECOG, <i>n</i> (%)					0.32
0	277 (49.7%)	10 (50.0%)	15 (68.2%)	252 (48.9%)	
1	227 (40.8%)	8 (40.0%)	5 (22.7%)	214 (41.6%)	
2	35 (6.3%)	1 (5.0%)	1 (4.5%)	33 (6.4%)	
3	13 (2.3%)	0 (0.0%)	1 (4.5%)	12 (2.3%)	
4	5 (0.9%)	1 (5.0%)	0 (0.0%)	4 (0.8%)	
WBC ( $\times 10^9/L$ ), median (IQR)	9.2 (2.9 - 41.2)	15.7 (4.6 - 98.4)	26.2 (3.7 - 82.2)	8.9 (2.7 - 39.9)	0.26
BM blast cells, median (IQR)	33.6 (9.0 - 64.0)	56.0 (51.5 - 74.5)	59.0 (26.0 - 80.5)	30.0 (8.0 - 61.5)	0.0007
Creatinine mg/dL, median (IQR)	0.8 (0.7 - 1.0)	0.8 (0.7 - 1.0)	0.9 (0.7 - 1.0)	0.8 (0.7 - 1.0)	0.77
WHO by Differentiation, <i>n</i> (%)					0.36
Minimal Differentiation	37 (10.0%)	0 (0.0%)	1 (6.2%)	36 (10.4%)	
Without+With Maturation	137 (37.1%)	7 (77.7%)	9 (56.3%)	121 (35.0%)	
Myelomonocytic	93 (25.1%)	0 (0.0%)	4 (25.0%)	89 (25.8%)	
Monocytic	85 (23.0%)	2 (22.2%)	2 (12.5%)	81 (23.5%)	
Erythroid	13 (3.5%)	0 (0.0%)	0 (0.0%)	13 (3.8%)	
Megacarioblastic	5 (1.4%)	0 (0.0%)	0 (0.0%)	5 (1.4%)	
MRC cytogenetic risk, <i>n</i> (%)					0.44
Favorable	41 (7.9%)	0 (0.0%)	1 (4.8%)	40 (8.3%)	
Intermediate	98 (19.0%)	4 (25.0%)	6 (28.6%)	88 (18.3%)	
Normal Karyotype	244 (47.2%)	10 (62.5%)	11 (52.4%)	223 (46.5%)	
Unfavorable	134 (25.9%)	2 (12.5%)	3 (14.3%)	129 (26.9%)	
Targetable mutations					

<i>FLT3, n (%)</i>	199 (28.6%)	7 (17.5%)	11 (26.2%)	181 (29.5%)	0.26
<i>IDH1, n (%)</i>	76 (10.9%)	2 (5.0%)	6 (14.3%)	68 (11.1%)	0.39
<i>IDH2, n (%)</i>	92 (13.2%)	2 (5.0%)	2 (4.8%)	88 (14.4%)	0.063
<i>KIT, n (%)</i>	28 (4.0%)	2 (5.0%)	0 (0.0%)	26 (4.2%)	0.43
<i>NPM1, n (%)</i>	208 (29.9%)	1 (2.5%)	12 (28.6%)	195 (31.8%)	< 0.0001
H SCT, <i>n (%)</i>					0.051
Allogeneic	163 (23.4.4%)	4 (10.0%)	9 (21.4%)	150 (24.4%)	
Autologous	45 (6.4%)	3 (7.5%)	0 (0.0%)	42 (6.8%)	
Treatment response					0.04
CR+CRi	426 (71.6%)	10 (83.3.3%)	17 (85.0%)	399 (70.9%)	
Partial remission	26 (4.4%)	2 (16.7%)	0 (0.0%)	24 (4.3%)	
Resistance	101 (17.0%)	0 (0.0%)	1 (5.0%)	100 (17.8%)	
Death	42 (7.1%)	0 (0.0%)	2 (10.0%)	40 (7.1%)	
No. of deaths, <i>n (%)</i>					< 0.0001
No	492 (70.7%)	39 (97.5%)	34 (81.0%)	419 (68.2%)	
Yes	204 (29.3%)	1 (2.5%)	8 (19.0%)	195 (31.8%)	

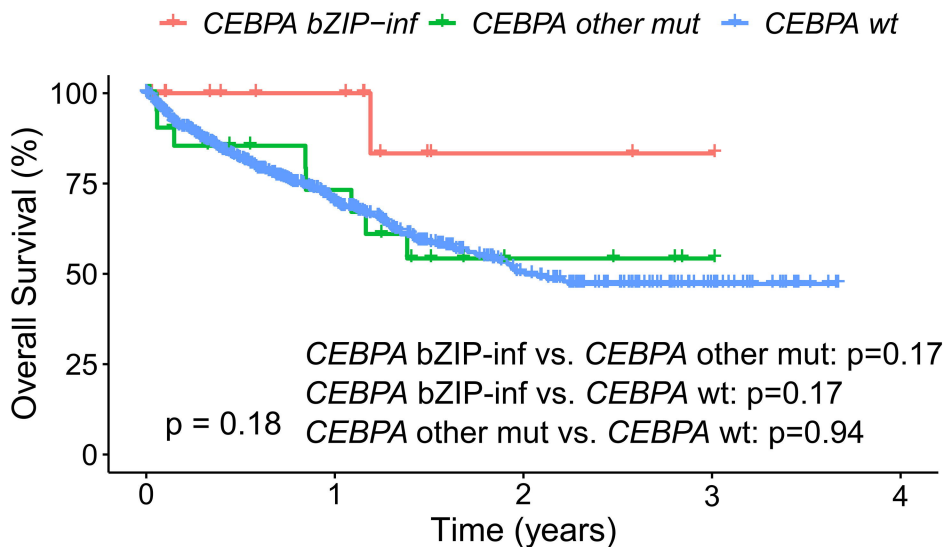
IQR: Interquartile-range; AML: Acute Myeloid Leukemia; ECOG: Eastern Cooperative Oncology Group; WBC: White Blood Cell; BM: Bone Marrow; MRC: Medical Research Council. HSCT: hematopoietic stem cell transplantation; CR: Complete Remission; CRi: Complete Remission with incomplete count recovery.

## FIGURE LEGENDS

**Figure 1.** Overall survival probability curves (%) of Intensively Treated acute Myeloid Leukemia (IT AML) patients: **A:** patients with mutation *CEBPA*-bZIP-inf (red line), with other *CEBPA* mutation (green line) and *CEBPA*wt mutation (blue line); **B:** patients with all *CEBPA*-bZIP mutations including non-inframe (*CEBPA* bZIP, red line), with *CEBPA* other mut (green line) and *CEBPA*wt (blue line).

**Figure 2.** Genomic characterization of *CEBPA* mutated patients: **A:** Co-mutational spectrum of the 82 patients with *CEBPA* mutations. Each column represents 1 subject. B). Comparison of percentage of patients with additional specific gene mutations between *CEBPA*-bZIP-inf and *CEBPA*other mut. **B:** Bradley-Terry model to infer the timing of co-mutation occurrence by using the Bradley-Terry model(11). As displayed *TP53* mutations, chromatin modifiers mutations (*ASXL1*, *EZH2*), epigenetic regulators (*TET2*, *DNMT3A*) and splicing machinery mutations (*SF3B1*, *UA2F1*) seem to occur earlier. By contrast, mutations in *NPM1* and signaling pathways (*NRAS*, *KRAS* and *FLT3*) seem to occur later.

A

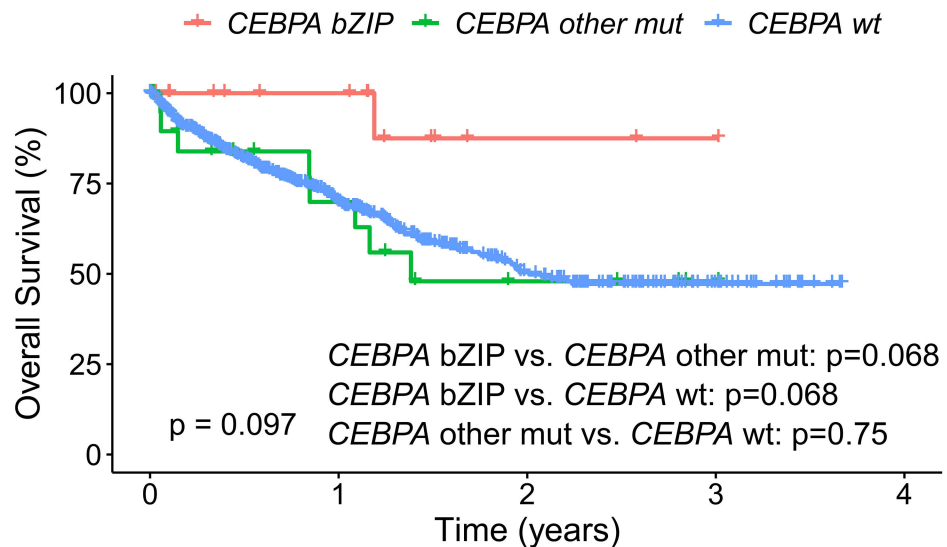
**CEBPA bZIP-inf**

Number at risk

CEBPA bZIP-inf	40	9	2	1	0
CEBPA other mut	42	12	4	1	0
CEBPA wt	614	234	83	23	0
	0	1	2	3	4

Time (years)

B

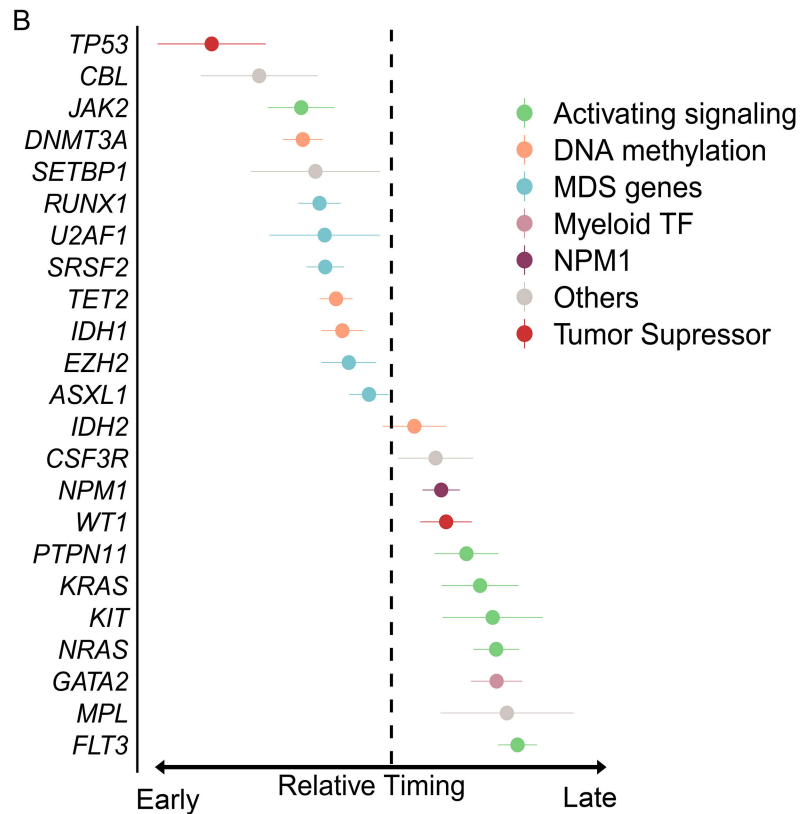
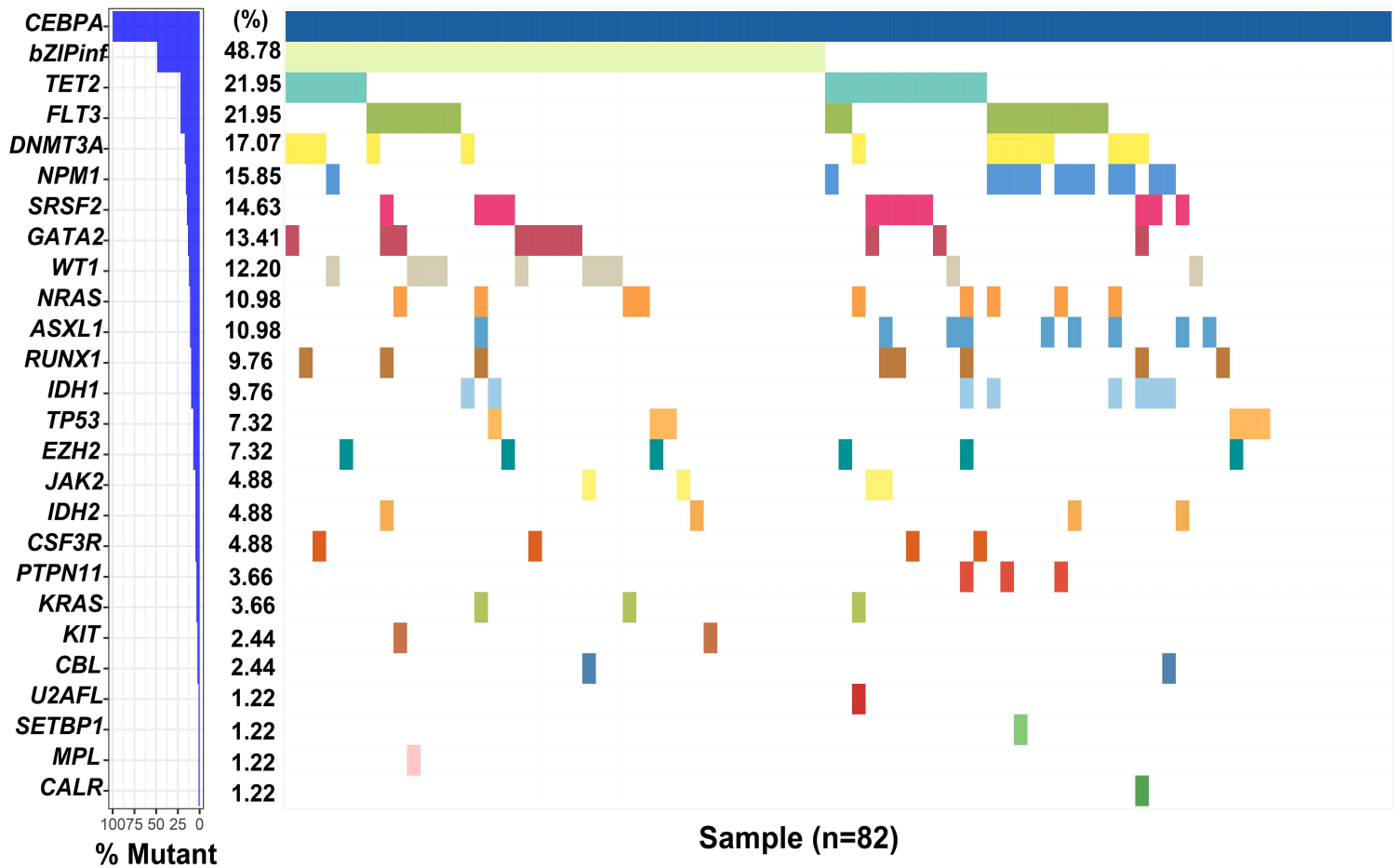
**CEBPA bZIP**

Number at risk

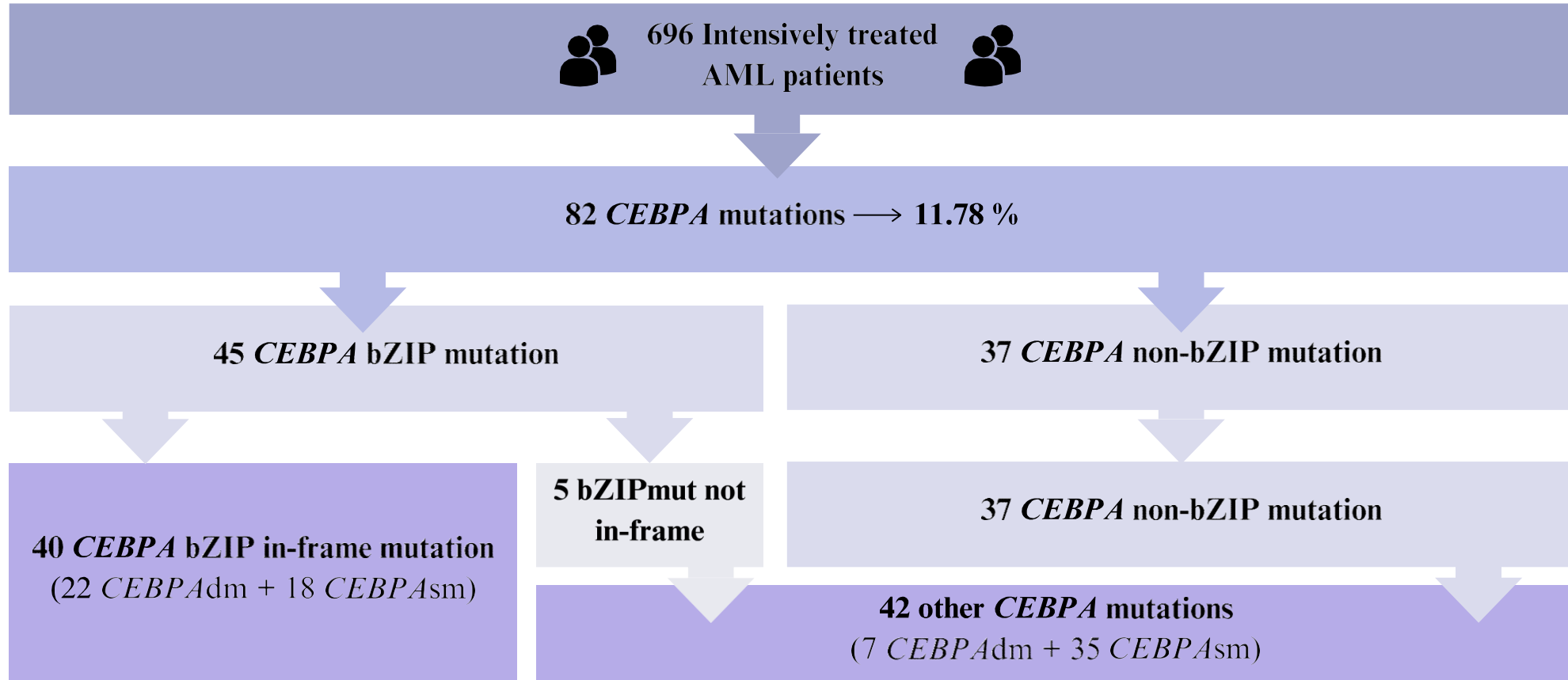
CEBPA bZIP	45	11	2	1	0
CEBPA other mut	37	10	4	1	0
CEBPA wt	614	234	83	23	0
	0	1	2	3	4

Time (years)

A



**Figure 1S.** Classification flow-chart of patients according to the presence of *CEBPA* mutations detected by NGS.



## APPENDIX

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