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

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 α (*CEBPA*) gene have classically classified as favorable risk.[3] The frequency of *CEBPA* gene mutations ranges from 7% to 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 World health Organization (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 *CEPBAdm*.[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=2,434 consecutive patients with available centralized NGS) involving seven Spanish central-core laboratories (PLATAFO-LMA protocol; *clinicaltrials gov. Identifier: NCT04446741)*. The consortium members are included in the *Online Supplementary Appendix*.

Of them, a total of 696 intensively treated AML (IT AML) patients (≥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 cytarabine (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 NGS 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 3 bp and affect DNA binding, fork or bZIP from amino acid position 278 to C-terminus as previously stated.[9]

A total of 82 of 696 IT AML patients (11.8%) harbored *CEBPA* gene mutations by NGS. Among them, 45 had mutations within bZIP domain and 40 fulfilled criteria of *CEBPA*-bZIP-inf (5.7%). Among *CEBPA*-bZIP-inf, 22 were *CEBPA*dm and 18 *CEBPA*sm. *Online Supplementary 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 the entire cohort according to *CEBPA* status (i.e, bZIP-inf *vs*. other *CEBPA* mutations [*CEBPA* other mut] *vs*. *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% confidence interval [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). In order 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 *CEBPA*wt (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 2; range, 0-7). Only 17 patients (13.69%) had no additional mutations. From these 17 patients (47% *CEBPA*-bZIP-inf), karyotype data was only available for five patients (2 patients had intermediate

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

	Total	*CEBPA* bZIPinf	*CEBPA* other mut	*CEBPA*wt	*P*
N	696	40	42	614	
Sex, N (%)					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 in years, 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, N (%)					< 0.001
>60 years	288 (41.4)	6 (15.0)	23 (54.8)	259 (42.2)	
<60 years	408 (58.6)	34 (85.0)	19 (45.2)	355 (57.8)	
Type of AML, N (%)					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, N (%)					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, N (%)					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)	
Erythorid	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, N (%)					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, N (%)					
FLT3	199 (28.6)	7 (17.5)	11 (26.2)	181 (29.5)	0.26
IDH1	76 (10.9)	2 (5.0)	6 (14.3)	68 (11.1)	0.39
IDH2)	92 (13.2)	2 (5.0)	2 (4.8)	88 (14.4)	0.063
KIT	28 (4.0)	2 (5.0)	0 (0.0)	26 (4.2)	0.43
NPM1	208 (29.9)	1 (2.5)	12 (28.6)	195 (31.8)	<0.0001
HSCT, N (%)					0.051
Allogeneic	163 (23.4)	4 (10.0)	9 (21.4)	150 (24.4)	
Autologous	45 (6.4)	3 (7.5)	0 (0.0)	42 (6.8)	
Treatment response, N (%)					
CR + CRi	426 (71.6)	10 (83.3)	17 (85.0)	399 (70.9)	
Partial remission	26 (4.4)	2 (16.7)	0 (0.0)	24 (4.3)	0.04
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, N (%)					<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; WHO: World Health Organization; inf: in-frame; mut: mutation; wt: wild-type.

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 modificators 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.

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 methologies.[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

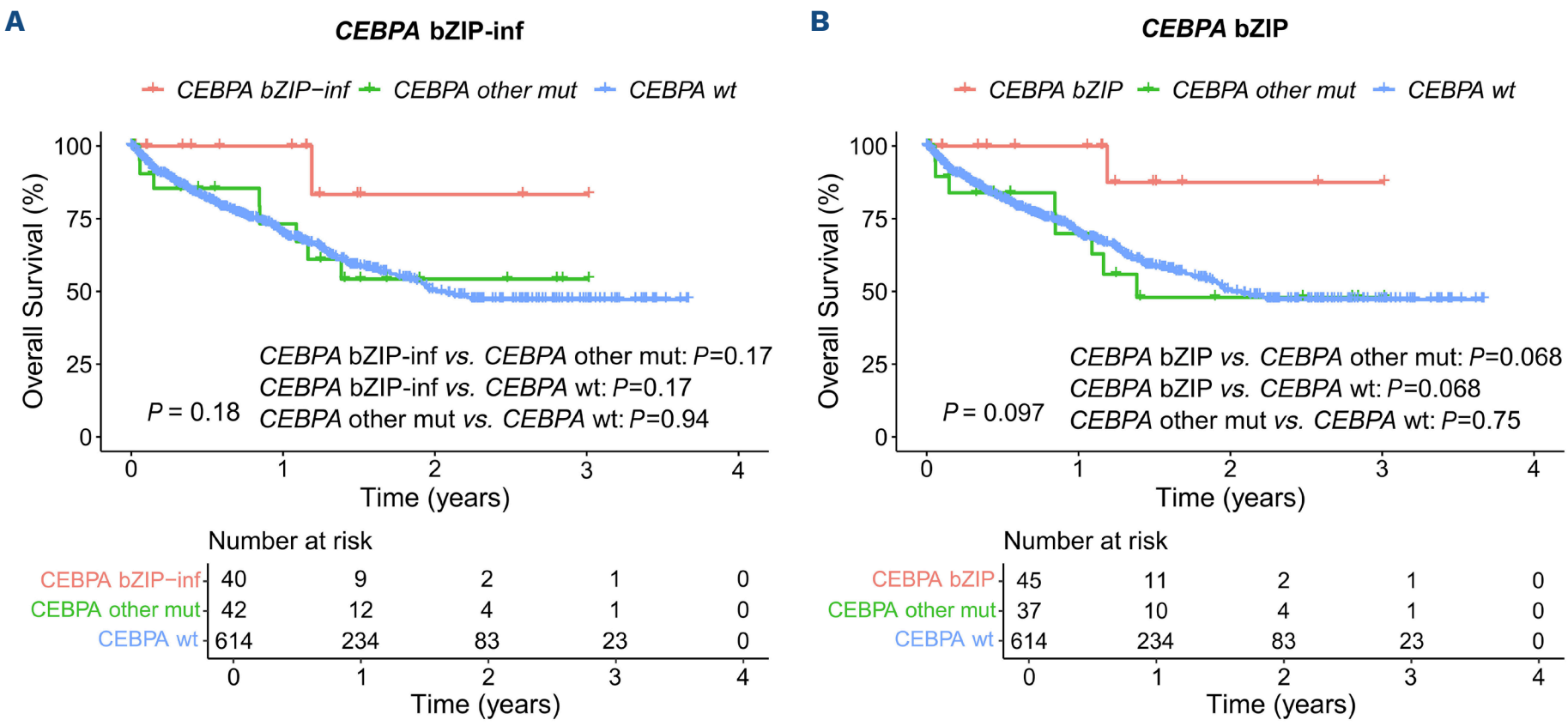
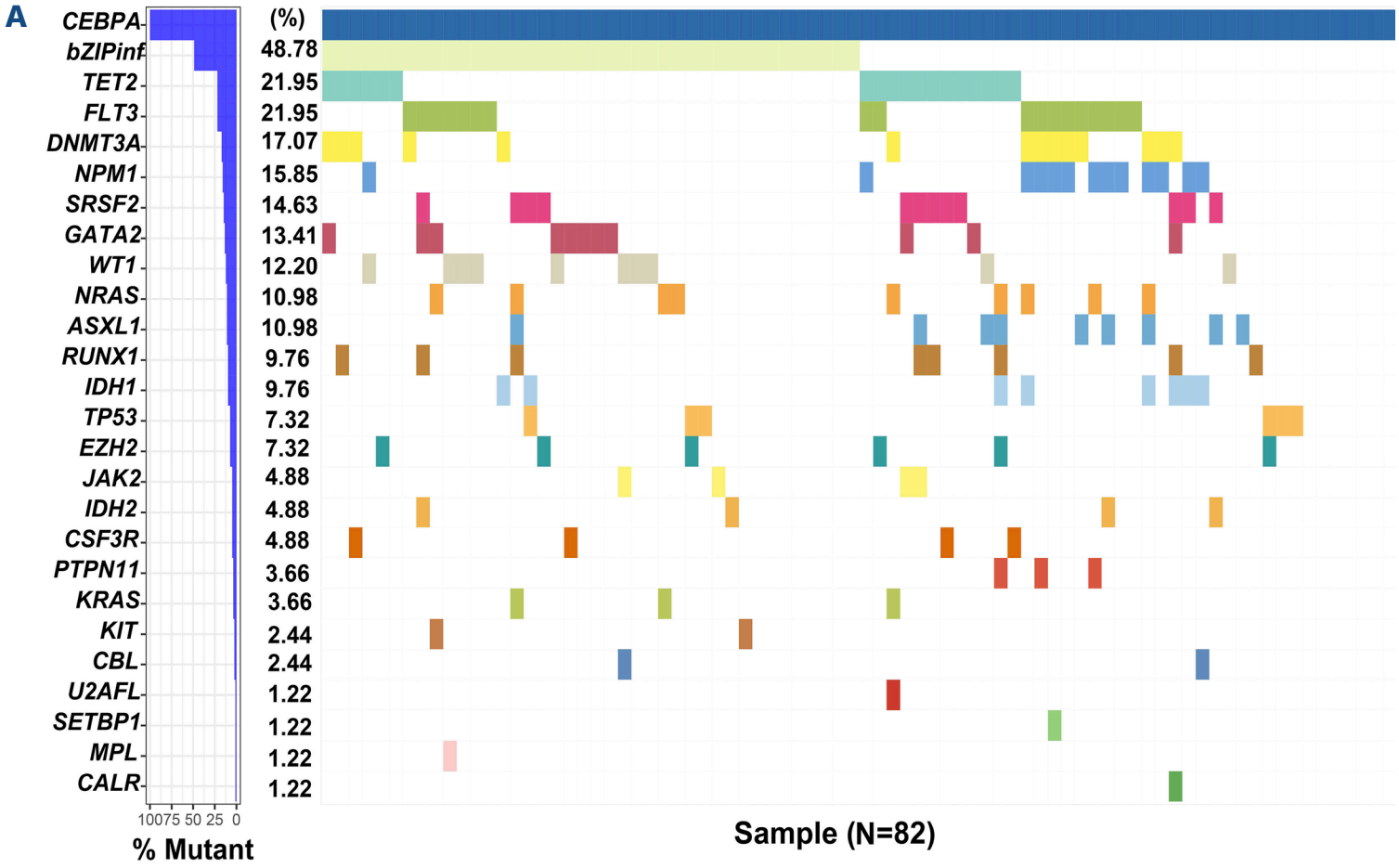


Figure 1. Overall survival probability curves (%) of intensively treated acute myeloid leukemia patients. (A) Patients with bZIP in-frame (inf) *CEBPA* mutation *CEBPA*-bZIP-inf (red line), with other *CEBPA* mutation (mut) (green line) and wild-type *CEBPA* (*CEBPAwt*) mutation (blue line). (B) Patients with all *CEBPA*-bZIP mutations including non-inframe (*CEBPA* bZIP, red line), with *CEBPA* other mut (green line) and *CEBPAwt* (blue line).

that *CEBPA* bZIP mutant does not downregulate miR-182 and this incapability could be restricted to typical bZIP-inf 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 *CEBPA*dm 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*



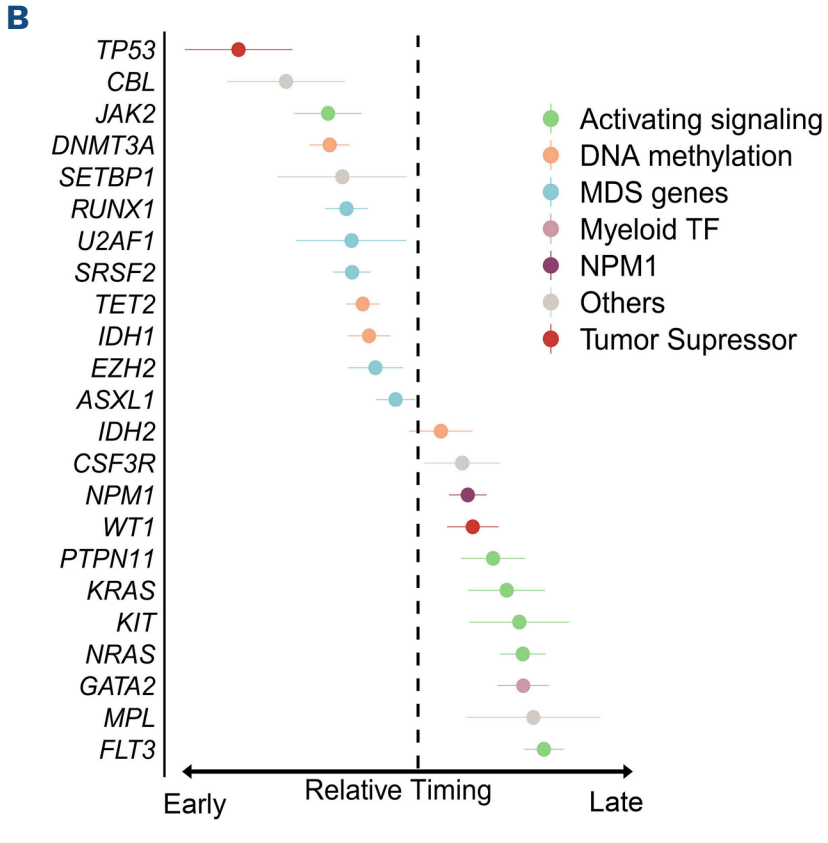


Figure 2. Genomic characterization of *CEBPA*-mutated patients. (A) Co-mutational spectrum of the 82 patients with *CEBPA* mutations. Each column represents 1 subject. (B) Comparison of percentage of patients with additional specific gene mutations between bZIP in-frame *CEBPA* mutation (*CEBPA*-bZIP-inf) and other *CEBPA* mutation (*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 modificators 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. MDS: myelodysplatic syndrome; TF: tissue factor.

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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Disclosures

No conflicts of interest to disclose.

Contributions

EPdlT, JS, JSG and PM conceived and designed the study, and wrote the manuscript. EPdlT and JS performed data analysis. JS, DMC, LT, CS, RA, CBS, MCC, MJL, ES, CAP, JMB, TB, CG, MT, LA, JMAD, ERA, PMS, AO, AMCA, CRM, SV, LH, JML, RGS, JAPS, MJC, MTGC and EB provided clinical and/molecular data of patients, collected and assembled data and interpreted data. All authors wrote the manuscript, gave the final approval of the manuscript and are accountable for all aspects of the work.

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Data-sharing statement

Requests for data sharing should be sent to Pau Montesinos (montesinos_pau@gva.es).

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