HHS Public Access

Author manuscript

*Leukemia*. Author manuscript; available in PMC 2018 October 26.

Published in final edited form as:

*Leukemia*. 2018 November ; 32(11): 2512–2518. doi:10.1038/s41375-018-0143-8.

# Blast Phase Chronic Myelomonocytic Leukemia: Mayo-MDACC Collaborative study of 171 cases

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**Keywords**

CMML; Blast phase disease; Survival

## To the Editor

Chronic myelomonocytic leukemia (CMML) is a clonal, hematopoietic stem cell disorder, characterized by sustained peripheral blood (PB) monocytosis and an inherent risk for blast phase (BP) disease.[1, 2] Blast phase, as defined by ≥20% PB or bone marrow (BM) blasts,[1] has a reported incidence ranging from 15% to 29%.[1, 2] Risk factors for CMML-BP have included high risk karyotype,[3, 4] PB blast %,[5, 6] circulating immature myeloid cells (IMC),[6] absolute monocyte count (AMC) >10 × 10(9)/L,[5, 6] *ASXL1, RUNX1, NRAS, SETBP1, DNMT3A* and *NPM1* mutations.[7, 8] In CMML, while predictors for BP have been identified, not much is known about prognostication, optimal treatment modalities and survival outcomes. We carried out this large, collaborative, two institution study (Mayo Clinic, Minnesota and the MD Anderson Cancer Center, Texas) with the intent to examine i) prognostic factors, ii) survival trends, and iii) treatment outcomes in patients with CMML-BP.

The diagnoses of CMML, and CMML-BP were according to the 2016 WHO criteria for hematological malignances.[1] CMML cytogenetic risk stratification was per the Mayo-French cytogenetic stratification system.[4] Over-all CMML risk stratification was based on the Mayo prognostic model, GFM model, and the Mayo Molecular Model.[8–10] Cytogenetic and molecular genetic risk stratification for CMML-BP cases was based on the 2017 European Leukemia Net (ELN) guidelines.[11] Response assessment to therapy was based on the International Working Group (IWG) MDS and MDS/MPN overlap syndrome response



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***Conflict of interest statements:*** None of the authors have any conflict of interest that is relevant to the current paper.

assessment criteria,[12, 13] while that for AML was based on the ELN response criteria.[11] Twenty-nine gene panel targeted capture assays were carried out on BM DNA specimens obtained at diagnosis for myeloid-relevant genes by previously described methods.[14] All statistical analyses considered parameters obtained at time of CMML and CMML-BP diagnosis. Differences in the distribution of continuous variables between categories were analyzed by either Mann-Whitney or Kruskal-Wallis test. Patient groups with nominal variables were compared by chi-square test. Cox proportional hazard regression model was used for multivariable analysis. The Stat View (SAS Institute, Cary, NC, USA) statistical package was used for all calculations. One hundred and seventy one patients with CMML-BP were included in the study; 84 (49%) seen at the Mayo Clinic and 87 (51%) at the MDACC (Supplementary table 1).

### i) Characteristics at CMML diagnosis

The median age at CMML diagnosis was 69 years (range, 27-90 years), with 64% ($n$=110) being male. Cytogenetic information at CMML diagnosis was available in 157 (92%) patients of which, 65 (41%) had an abnormal karyotype (supplementary table two). Archived DNA at CMML diagnosis was available in 67(39%) patients (table 1) and encountered mutations included; *ASXL1* 43%, *SRSF2* 30%, *TET2* 30%, *NRAS* 15%, *RUNX1* 12%, *DNMT3A* 10%, *IDH2* 10%, *SETBP1* 9%, *CBL* 7%, *JAK2*V617F 6%, *U2AF1*, *PTPN11, NPM1* and *Tp53* 4% each, *c-KIT*, and *FLT3 ITD* 3% each, *KRAS*, *CSF3R, MPL, SF3B1, ZRSR2, IDH1* and *EZH2* 1% each, respectively. Eight one (47%) patients received prior hypomethylating agent (HMA) therapy (Decitabine 50, 5-azacitidine 31), for a median number of 4 cycles (range 1-19 cycles), with 33% having achieved a complete remission (CR) prior to CMML-BP (table 1).

### ii) Characteristics at CMML-BP transformation

The median age at CMML-BP was 71 years (range, 28-91) (supplementary table 3). Cytogenetic data at CMML-BP was available in 139 (81%) patients and risk stratification by the ELN criteria included, 2 (1%) favorable, 91 (65%) intermediate and 46 (33%) adverse risk, respectively. Forty-nine (35%) patients had a normal karyotype, while the 2 patients with favorable risk karyotypes had inversion (16)(p13;1q22) and t(16;16)(p13.1q22), respectively. Adverse karyotypes included; monosomal karyotype 18 (13%), complex karyotype 17 (12%), -7/del7q 10 (7%), 11q23 *KMT2A* translocations 2 (1%), and one each with inversion (3)(q21.3q26.2) [*GATA2-EVI1*] (0.5%) and isochromosome 17q, respectively. Archived DNA at CMML-BP was available on 22 (13%) patients and the mutational frequencies were; *TET2* 50%, *ASXL1* 45%, *NRAS* and *RUNX1* 36% each, *IDH2* 32%, *IDH1* 27%, *EZH2* 23%, *SRSF2* 22%, *JAK2* V617F 14%, *FLT3* ITD 13%, 6% each for *U2AF1, ZRSR2, KRAS, PTPN11, c-KIT* and *Tp53, CBL* 5% and *NPM1* 4% (Supplementary table 3). Cytogenetic clonal evolution was seen in 41 (24%) patients, while molecular clonal evolution was seen in 9 (50%) of 18 assessable patients.

### iii) CMML-BP treatment strategies and responses

Treatment details were available in 157 (92%) patients and included best supportive care 39 (BSC, 25%), HMA therapy 16 (10%), AML-like induction chemotherapy 59 (38%), AML-like induction chemotherapy followed by allogeneic HCT 23 (15%), upfront allogeneic HCT

2 (2%) and clinical trials in 18 (11%) (Supplementary table 4). Twenty nine (38%) patients had prior 5-azacitidine exposure for a median of 6 cycles (range, 2-24), while 50 (65%) patients had prior decitabine exposure for a median of 12 cycles (range, 1-50), with 2 patients having received both agents sequentially. In the azacitidine treated patients 33% achieved a CR, 11% a partial response (PR), 48% had stable disease, while 8% had disease progression on therapy. In the decitabine treated patients, 60% had a CR, 12% PR, 21% stable disease, while 7% had disease progression on therapy. Among the 8 patients that went on to get post CMML-BP HMA therapy, 4 (50%) had received prior azacitidine with all 4 having stable disease, while 4 (50%) had received decitabine with 50% CR, 25% PR and 25% with stable disease. Twenty five (16%) patients went on to receive HCT, with 40% being in a CR and 12% having CRi at the time of HCT (supplementary table 5). At last follow up, 19 (76%) deaths were reported, with a median relapse free survival (RFS) of 7 months and a median OS of 10 months; with no difference in RFS (p=0.8) or OS (p=0.7) between patients that received a MA versus RIC. CMML-BP-treatment response was assessable in 113 (72%) patients, including 55 (93%) treated with AML-like induction chemotherapy, 25 (100%) with allogeneic HCT, 16 (100%) with HMA and 16 (89%) enrolled in clinical trials; with respective CR rates of 13%, 48%, 0% and 6%.

### iv) CMML-BP survival outcomes

After a median follow-up of 4.4 months (range 0-122), 141 (82%) deaths were recorded. Median OS was 6 months with 1-, 3- and 5-year survival rates of 25%, 9% and 6%, respectively. Survival trends were similar (p=0.4) for patients diagnosed prior to and after the year 2006 (figure 1A). In patients that received AML-like induction chemotherapy ($n$=55), survival outcomes were dismal regardless of response (figure 1B). Similarly, with the exception for a modest survival benefit for patients undergoing allogeneic HCT (5-year survival rate 21%), survival with BSC, AML-like induction chemotherapy alone, HMA and clinical trials was dismal (figure 1C). In the allogeneic HCT group, patients that had ELN adverse risk cytogenetics at CMML-BP had an even shorter survival in comparison to those with ELN intermediate risk cytogenetics (figure 1D). Ninety two % of post HCT deaths were due to disease relapse.

In univariate analysis of variables recorded at time of CMML-BP, risk factors adversely impacting survival included older age (p=0.04), lower hemoglobin (p=0.02), PB blast % (<0.0001), ELN high risk cytogenetics (p=0.007), prior exposure to HMA (p=0.006), failure to achieve CR/CRi (p=0.0006), and not undergoing HCT (p=0.0011). Gene mutations, including *FLT3*-ITD (p=0.4), cytogenetic clonal evolution (p=0.3), and molecular clonal evolution (p=0.4), did not impact survival. In multivariable analysis, only PB blast % (PB blasts≥20%, p=0.0005, HR 2.2, 95% CI 1.4-3.4), prior exposure to HMA therapy (p=0.002, HR 1.9, 95% CI 1.2-2.1), ELN high risk cytogenetics (p=0.03, HR 1.5 (95% CI 1.1-2.3) and failure to achieve CR/CRi (p=0.02, HR 1.4; 95% CI 1.2-3.4) retained independent prognostic value.

CMML-BP is associated with high morbidity and poor outcomes.[2, 8, 14] In this study of 171 CMML-BP patients the median OS was 6 months with a 5-year survival rate of 6%. Although with time, advances have occurred in clinical therapeutics; in our study survival in

CMML-BP was not significantly different based on the calendar year of diagnosis. CMML-BP patients were treated with a variety of modalities and with the exception for a modest survival benefit with allogeneic HCT (5-year survival rate 21%), survival outcomes with all other modalities remained dismal (5-year survival rates <10%). Eight one (47%) patients had prior exposure to HMA with 33% having achieved CR prior to CMML-BP; indicating the ineffectiveness of these agents in altering the natural course of this disease. In a recent study, serial sequencing demonstrated that responses to HMA in CMML were associated with changes in DNA methylation and gene expression, without any changes in the mutational allele burdens.[15]

In the current study, we demonstrate that prior exposure to HMA was an independent factor adversely impacting post CMML-BP survival; although one may argue that these patients already had aggressive disease biology, necessitating the earlier use of HMA. Additional negative prognosticators included ELN high risk cytogenetics, PB blast % ≥20 and failure to achieve CR/CRi with induction chemotherapy. Neither did cytogenetic clonal evolution, nor molecular clonal evolution, impact survival. Although, the achievement of CR/CRi after induction chemotherapy was found to have a favorable impact, the overall durability of response was limited (median OS 9.8 months). Allogeneic HCT was successfully carried out in a small fraction of CMML-BP patients (15%); with patients that had adverse cytogenetic findings at CMML-BP demonstrating a trend towards inferior survival. This data supports the earlier use of allogeneic HCT in eligible patients, preferably before blast phase disease. The response rates to HMA use after CMML-BP was strikingly dismal with 0% CR and 17% CRi; suggesting that these patients should not be reexposed to these agents.

In summary, ours is the largest-to-date study, describing the clinical and molecular correlates and dismal outcomes of patients with CMML-BP disease. These results serve as a critical benchmark for future clinical trial design and conduct.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

Current publication is supported in part by grants from the “The Gerstner Family Career Development Award” and the Mayo Clinic Center for Individualized Medicine, Mayo Clinic, Rochester, MN, USA”.

This publication was supported by CTSA Grant Number KL2 TR000136 from the National Center for Advancing Translational Science (NCATS). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

This work is supported in part by the University of Texas MD Anderson Cancer Center Support Grant CA016672, the University of Texas MD Anderson MDS/AML Moon Shot, and the MDS Clinical Research Consortium, which is funded by the Edward P. Evans Foundation.

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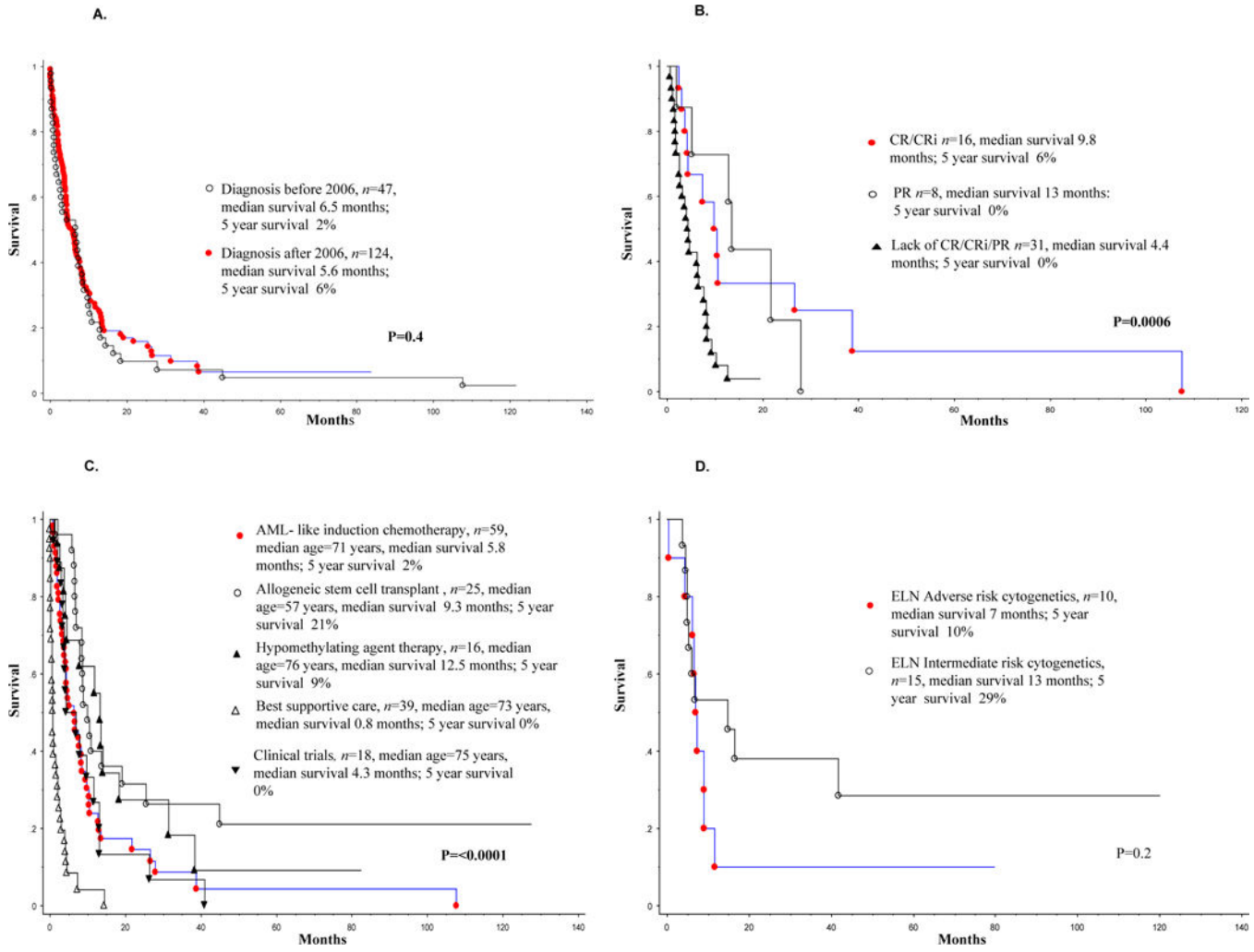


**Figure one.**

Figure 1A: Survival of 171 patients with chronic myelomonocytic leukemia – blast phase (CMML-BP) stratified by year of diagnosis.

Figure 1B: Survival of 55 patients with chronic myelomonocytic leukemia- blast phase who received AML-like induction chemotherapy without allogeneic stem cell transplantation; stratified by type of response achieved.

Figure 1C: Survival of 157 patients with chronic myelomonocytic leukemia- blast phase stratified by type of therapy received.

Figure 1D: Survival of 25 patients with chronic myelomonocytic leukemia- blast phase who received allogeneic stem cell transplantation, stratified by cytogenetics at blast phase transformation.

## Table 1

Presenting clinical and laboratory characteristics of 171 patients with chronic myelomonocytic leukemia (CMML) at CMML diagnosis, stratified by whether or not they received hypomethylating agent therapy before CMML blast phase disease

| Variables | All patients with CMML (n=171) | CMML patients that received HMA before CMML-BP (n=81, 47%) | CMML patients that did not receive HMA before CMML-BP (n=90, 53%) | P value |
|---|---|---|---|---|
| Age in years; median (range) | 69 (27-90) | 70 (45-85) | 68 (27-90) | 0.09 |
| Males; *n* (%) | 110 (64) | 54 (67) | 56 (62) | 0.5 |
| Hemoglobin, g/dL; median (range) | 10.6 (1.4-15.8) | 10.6 (6.8-15.8) | 10.6 (1.4-14.9) | 0.9 |
| WBC × $10^9$/L; median (range) | 13.8 (1.3-265) | 15 (2.7-79) | 12.7 (1.3-265) | 0.6 |
| ANC × $10^9$/L; median (range) | 6.5 (0.2-143) | 7.1 (0.2-50.6) | 5.7 (0.2-143) | 0.08 |
| AMC × $10^9$/L; median (range) | 2.9 (0-34.4) | 2.9 (0-34.4) | 2.9 (0.1-26) | 0.8 |
| ALC × $10^9$/L; median (range) | 2.1 (0.4-22) | 2.1 (0.4-11.9) | 2.3 (0.4-22) | 0.9 |
| Platelets × $10^9$/L; median (range) | 100 (10-726) | 88 (14-497) | 112 (10-726) | 0.08 |
| Presence of circulating immature myeloid cells; *n* (%) | 109 (64) | 52 (64) | 57 (63) | 0.9 |
| PB blast %; median (range) | 0 (0-19) | 0 (0-14) | 0 (0-19) | 0.3 |
| BM blast %; median (range) | 5 (0-19) | 6 (1-18) | 3 (0-19) | 0.09 |
| Lactate dehydrogenase levels IU/ml; median (range) | 506 (109-4522) | 626 (109-4522) | 385 (111-2046) | **<0.0001** |
| FAB CMML subtype | (*n*=170) | | (*n*=89) | |
| Proliferative | 89 (52) | 46 (57) | 43 (48) | 0.3 |
| Dysplastic | 81 (48) | 35 (43) | 46 (52) | |
| Therapy related CMML; Yes, *n* (%) | 26 (15) | 10 (12) | 16 (18) | 0.3 |
| Next generation sequencing analysis; *n* (%) | (*n* =67) | (*n* =28) | (*n* =39) | |
| ***1. Epigenetic regulators*** | | | | |
| *TET2* | 20 (30) | 2 (7) | 18 (46) | **0.0006** |
| *DNMT3A* | 7 (10) | 2 (7) | 5 (13) | 0.5 |
| *IDH1* | 1 (2) | 0 | 1 (3) | 0.4 |
| *IDH2* | 7 (10) | 4 (14) | 3 (8) | 0.4 |
| ***2. Chromatin regulation*** | | | | |
| *ASXL1* | 29 (43) | 8 (29) | 21 (54) | **0.04** |
| *EZH2* | 1 (1) | 1 (4) | 0 | 0.2 |
| ***3. Transcription factors*** | | | | |

| Variables | All patients with CMML (n=171) | CMML patients that received HMA before CMML-BP (n=81, 47%) | CMML patients that did not receive HMA before CMML-BP (n=90, 53%) | P value |
|---|---|---|---|---|
| *RUNX1* | 8 (12) | 2 (7) | 6 (15) | 0.3 |
| ***4. Spliceosome components*** | | | | |
| *SF3B1* | 1 (1) | 0 | 1 (3) | 0.4 |
| *SRSF2* | 20 (30) | 6 (21) | 14 (36) | 0.2 |
| *U2AF1* | 3 (4) | 1 (4) | 2 (5) | 0.8 |
| *ZRSR2* | 1 (1) | 0 | 1 (3) | 0.4 |
| ***5. Cell signaling*** | | | | |
| *JAK2 V617F* | 4 (6) | 1 (4) | 3 (8) | 0.5 |
| *MPL* | 1 (1) | 1 (4) | 0 | 0.2 |
| *CBL* | 5 (7) | 1 (4) | 4 (10) | 0.3 |
| *NRAS* | 10 (15) | 3 (11) | 7 (18) | 0.4 |
| *KRAS* | 1 (1) | 1 (4) | 0 | 0.2 |
| *PTPN11* | 3 (4) | 1 (4) | 2 (5) | 0.8 |
| *CSF3R* | 1 (1) | 0 | 1 (3) | 0.4 |
| *C-KIT* | 2 (3) | 2 (7) | 0 | 0.09 |
| *FLT3* | 2 (3) | 1 (4) | 1 (3) | 0.8 |
| *NPM1* | 3 (4) | 2 (7) | 1 (3) | 0.4 |
| ***6. Tumor suppressor genes*** | | | | |
| *Tp53* | 3 (4) | 1 (4) | 2 (5) | 0.8 |
| ***7. Others*** | | | | |
| *SETBP1* | 6 (9) | 1 (4) | 5 (13) | 0.2 |
| ***8. PCR based gene sequencing*** | | | | |
| *FLT3ITD* | 2 (4) (*n*=47) | 2 (5) (*n*=39) | 0 (*n*=8) | 0.7 |
| *FLT3TKD* | 1 (2) (*n*=47) | 1 (3) (*n*=39) | 0 (*n*=8) | 0.7 |
| *CEBPA* | 2 (25) (*n*=8) | 0 (*n*=5) | 2 (67) (*n*=3) | **0.04** |
| *NRAS* | 9 (21) (*n*=43) | 8 (23) (*n*=35) | 1 (13) (*n*=8) | 0.5 |
| *KRAS* | 1 (2) (*n*=42) | 0 (*n*=34) | 1 (13) (*n*=8) | **0.04** |
| 2016 WHO CMML subtypes; *n* (%) | (*n*=170) | (*n*=81) | (*n*=89) | 0.6 |
| CMML-0 | 68 (40) | 29 (36) | 39 (44) | |
| CMML-1 | 38 (22) | 19 (23) | 19 (21) | |
| CMML-2 | 64 (38) | 33 (41) | 31 (35) | |
| Spanish Cytogenetic risk stratification; *n* (%) | (*n*=157) | (*n*=78) | (*n*=79) | 0.4 |
| Low | 97 (62) | 52 (67) | 45 (57) | |
| Intermediate | 22 (14) | 10 (13) | 12 (15) | |
| High | 38 (24) | 16 (21) | 22 (28) | |
| Mayo-French cytogenetic risk stratification; *n* (%) | (*n*=157) | (*n*=78) | (*n*=79) | 0.4 |
| Low | 97 (62) | 52 (67) | 45 (57) | |
| Intermediate | 46 (29) | 19 (24) | 27 (34) | |

| Variables | All patients with CMML (n=171) | CMML patients that received HMA before CMML-BP (n=81, 47%) | CMML patients that did not receive HMA before CMML-BP (n=90, 53%) | P value |
|---|---|---|---|---|
| High | 14 (9) | 7 (9) | 7 (9) | |
| Mayo prognostic model; *n* (%) | (*n*=167) | (*n*=81) | (*n*=86) | **0.005** |
| Low | 14 (8) | 3 (4) | 11 (13) | |
| Intermediate | 43 (26) | 15 (19) | 28 (33) | |
| High | 110 (66) | 63 (78) | 47 (55) | |
| Molecular Mayo model; *n* (%) | (*n*=50) | (*n*=16) | (*n*=34) | 0.2 |
| Low | 4 (8) | 1 (6) | 3 (9) | |
| Intermediate-1 | 8 (16) | 0 | 8 (24) | |
| Intermediate-2 | 16 (32) | 7 (44) | 9 (26) | |
| High | 22 (44) | 8 (50) | 14 (41) | |
| GFM CMML prognostic model; *n* (%) | (*n*=52) | (*n*=15) | (*n*=37) | 0.8 |
| Low | 19 (37) | 6 (40) | 13 (35) | |
| Intermediate | 22 (42) | 7 (47) | 15 (41) | |
| High | 11 (21) | 2 (13) | 9 (24) | |
| Deaths; *n* (%) | 141 (82) | 70 (86) | 71 (79) | 0.2 |
| Follow up in months; median (range) | 20 (1.5-135) | 25 (6-135) | 14 (1.5-135) | **0.0008** |

Key: CMML, chronic myelomonocytic leukemia, BP, blast phase, HMA, hypomethylating agent; WBC, white blood cell count; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; PB, peripheral blood; BM, bone marrow; WHO, World Health Organization; FAB, French–American–British classification; GFM, Groupe Francophone des Myélodysplasies.

** No information was available for NGS based *SUZ12, CALR, SH2B3, BCOR* mutational status