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

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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 × 10⁹/L,⁵,⁶ ASXL1, RUNXI, 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
assessment criteria,\textsuperscript{12, 13} while that for AML was based on the ELN response criteria.\textsuperscript{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.\textsuperscript{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, KRA\$, CSF3R, MPL, SF3B1, ZR\$, 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; monosomosomal karyotype 15 (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, ZR\$, KR\$, 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. 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.\textsuperscript{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 % $\geq$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.

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References

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19; 127(20):2391–2405. [PubMed: 27069254]
2. Patnaik MM, Wassie EA, Lasho TL, Hanson CA, Ketterling R, Tefferi A. Blast transformation in chronic myelomonocytic leukemia: Risk factors, genetic features, survival, and treatment outcome. Am J Hematol. 2015 May; 90(5):411–416. [PubMed: 25645147]

3. Such E, Germing U, Malcovati L, Cervera J, Kuendgen A, Della Porta MG, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood. 2013 Apr 11; 121(15):3005–3015. [PubMed: 23372164]

4. Wassie EA, Itzykson R, Lasho TL, Kosmider O, Finke CM, Hanson CA, et al. Molecular and prognostic correlates of cytogenetic abnormalities in chronic myelomonocytic leukemia: a Mayo Clinic-French Consortium Study. Am J Hematol. 2014 Dec; 89(12):1111–1115. [PubMed: 25195656]

5. Patnaik MM, Padron E, LaBorde RR, Lasho TL, Finke CM, Hanson CA, et al. Mayo prognostic model for WHO-defined chronic myelomonocytic leukemia: ASXL1 and spliceosome component mutations and outcomes. Leukemia. 2013 Jul; 27(7):1504–1510. [PubMed: 23531518]

6. Patnaik MM, Itzykson R, Lasho TL, Kosmider O, Finke CM, Hanson CA, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. Leukemia. 2014 Nov; 28(11):2206–2212. [PubMed: 24695057]

7. Patnaik MM, Barraco D, Lasho TL, Finke CM, Hanson CA, Ketterling RP, et al. DNMT3A mutations are associated with inferior overall and leukemia-free survival in chronic myelomonocytic leukemia. Am J Hematol. 2017 Jan; 92(1):56–61. [PubMed: 27733013]

8. Patnaik MM, Itzykson R, Lasho TL, Kosmider O, Finke CM, Hanson CA, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. Leukemia. 2014 Nov; 28(11):2206–2212. [PubMed: 24695057]

9. Itzykson R, Kosmider O, Renneville A, Gelsi-Boyer V, Meggendorfer M, Morabito M, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol. 2013 Jul 1; 31(19):2428–2436. [PubMed: 23690417]

10. Patnaik MM, Padron E, LaBorde RR, Lasho TL, Finke CM, Hanson CA, et al. Mayo prognostic model for WHO-defined chronic myelomonocytic leukemia: ASXL1 and spliceosome component mutations and outcomes. Leukemia. 2013 Jul; 27(7):1504–1510. [PubMed: 23531518]

11. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017 Jan 26; 129(4):424–447. [PubMed: 27895058]

12. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006 Jul 15; 108(2):419–425. [PubMed: 16609072]

13. Savona MR, Malcovati L, Komrokji R, Tiu RV, Mughal TI, Orazi A, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015 Mar 19; 125(12):1857–1865. [PubMed: 25624319]

14. Patnaik MM, Lasho TL, Vijayvargiya P, Finke CM, Hanson CA, Ketterling RP, et al. Prognostic interaction between ASXL1 and TET2 mutations in chronic myelomonocytic leukemia. Blood Cancer J. 2016 Jan 15.6:e385. [PubMed: 26718111]

15. Merlevede J, Droin N, Qin T, Meldi K, Yoshida K, Morabito M, et al. Mutation allele burden remains unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents. Nat Commun. 2016; 7:10767. [PubMed: 26908133]
**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 (0.3-34.4)                  | 2.9 (0.3-34.4)                                             | 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

| 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 (%)** |       |                                                          |                                                                 |         |
| 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 (%)** |       |                                                          |                                                                 |         |
| Low                | 97 (62)                        | 52 (67)                                                  | 45 (57)                                                         | 0.4     |
| Intermediate       | 22 (14)                        | 10 (13)                                                  | 12 (15)                                                         |         |
| High               | 38 (24)                        | 16 (21)                                                  | 22 (28)                                                         |         |
| **Mayo-French cytogenetic risk stratification; n (%)** |       |                                                          |                                                                 |         |
| Low                | 97 (62)                        | 52 (67)                                                  | 45 (57)                                                         | 0.4     |
| 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)                                                         | 0.005   |
| Low                                            | (n=167)                       | (n=81)                                                  | (n=86)                                                        |         |
| Intermediate                                   | 14 (8)                        | 3 (4)                                                   | 11 (13)                                                       |         |
| High                                           | 43 (26)                       | 15 (19)                                                 | 28 (33)                                                       |         |
| Mayo prognostic model; n (%)                   | (n=167)                       | (n=81)                                                  | (n=86)                                                        |         |
| Low                                            | 14 (8)                        | 3 (4)                                                   | 11 (13)                                                       |         |
| Intermediate                                   | 43 (26)                       | 15 (19)                                                 | 28 (33)                                                       |         |
| High                                           | 110 (66)                      | 63 (78)                                                 | 47 (55)                                                       |         |
| Intermediate                                   | 43 (26)                       | 15 (19)                                                 | 28 (33)                                                       |         |
| Molecular Mayo model; n (%)                    | (n=50)                        | (n=16)                                                  | (n=34)                                                        | 0.2     |
| Low                                            | 4 (8)                         | 1 (6)                                                   | 3 (9)                                                         |         |
| Intermediate                                   | 16 (32)                       | 7 (44)                                                  | 9 (26)                                                        |         |
| High                                           | 22 (44)                       | 8 (50)                                                  | 14 (41)                                                       |         |
| Intermediate                                   | 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.**

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