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ASXL1 mutation is associated with poor prognosis and acute transformation in chronic myelomonocytic leukaemia

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Running title: Gene mutations in CMML

Summary

Chronic myelomonocytic leukemia (CMML) is a haematological disease currently classified in the category of myelodysplastic syndromes/myeloproliferative neoplasm (MDS/MPN) because of its dual clinical and biological presentation. The molecular biology of CMML is poorly characterised. We studied a series of 53 CMML samples including 31 cases of myeloproliferative form (MP-CMML) and 22 cases of myelodysplastic forms (MD-CMML) using array-comparative genomic hybridisation (aCGH) and sequencing of 13 candidate genes including *ASXL1, CBL, FLT3, IDH1, IDH2, JAK2, KRAS, NPM1, NRAS, PTPN11, RUNX1, TET2* and *WT1*. Mutations in *ASXL1* and in the genes associated with proliferation (*CBL, FLT3, PTPN11, RAS*) were mainly found in MP-CMML cases. Mutations of *ASXL1* correlated with an evolution toward an acutely transformed state: all CMMLs that progressed to acute phase were mutated and none of the unmutated patients had evolved to acute leukaemia. The overall survival of *ASXL1* mutated patients was lower than that of unmutated patients.

Keywords: chronic myelomonocytic leukaemia, gene mutation, ASXL1, prognosis.

Chronic myelomonocytic leukaemia (CMML) is a haematopoietic disease currently classified by the WHO organization in a mixed category called MDS/MPN (myelodysplastic syndromes/myeloproliferative neoplasm) (Vardiman, 2002). Despite recent molecular improvements in the classification of myeloid neoplasms, diagnosis of CMML is still based on cytological criteria including persistent peripheral monocytosis greater than 1 x 10^9 /L, less than 20% blasts in the blood or bone marrow (BM) and bone marrow dysplasia in one or more myeloid lineage. The only molecular criterium is the absence of *BCR-ABL* transcript (Bennett *et al,* 1982, Vardiman, 2002). Because the blast number is a prognostic factor, CMML is divided in two types: type 1 with fewer than 5% blasts in the blood and 10% blasts in the bone marrow, and type 2 with between 5 to 19% in the blood or 10 to19% in the bone marrow (Vardiman, 2002; Vardiman *et al,* 2009).

Classification of CMML has always been a matter of debate based on the two distinct clinical presentations: dysplastic with symptomatic complications of cytopenia, and proliferative with splenomegaly or hepatomegaly. In 1994, on the basis of an arbitrary threshold of peripheral leukocyte count (WBC), a dysplastic (<13 x 10^9 /L) and a proliferative (> 13 x 10^9 /L) forms have been recognised by the FAB group (Bennett, 1994), which we will call here MD-CMML and MP-CMML, respectively. Until recently, neither biologic nor prognostic data allowed the support of this distinction except that MP-CMML seemed to have more *RAS* mutations (Padua *et al*, 1988; Padua *et al*, 1998). Recently, new molecular alterations have been described in CMML. We and others have showed a high frequency of *RUNX1* and *TET2* mutations (Gelsi-Boyer *et al,* 2008; Kosmider *et al,* 2009b; Kuo *et al,* 2009). Mutations of *TET2* and *CBL* occur in 50% (Kosmider *et al,* 2009b) and 5%

(Makishima *et al,* 2009) of CMML cases, respectively. Recently, we described exon 12 mutations of *ASXL1* with a frequency about 44% (Gelsi-Boyer *et al,* 2009). Currently, the impact of these alterations remains to be determined and the biological and clinical presentations are still heterogeneous and benefit from opposite therapeutics: cytotoxic in the MP form, haematopoietic growth factors in the MD form.

We propose here a comprehensive study of molecular alterations in a series of 53 CMMLs using genome-wide, high-density array-comparative genomic hybridisation (aCGH) and exon-coding sequencing of 13 candidate genes. We show that *ASXL1* mutations are associated with MP-CMML and that MP-CMMLs have overall more alterations. Most importantly, we show that mutations in *ASXL1* correlate with acute transformation of CMML and that the overall survival rate is lower in *ASXL1* mutated patients than in unmutated patients.

Patients and methods

Patients and samples

A series of consecutive bone marrow samples obtained from 53 patients, who all signed an informed consent, were collected. Among these were 31 MP-CMMLs and 22 MD-CMMLs as initially defined by the FAB group with a leukocyte count superior or inferior to 13 x 10^9 /L, respectively. The median age and leukocytosis were 74 years and 30 x 10^9 /L respectively in the MP-CMML group and 76.5 years and 9 x 10^9 /L respectively in the MD-CMML group. The main clinical and biological data of the 53 samples are presented in **Supplementary Table I.** Most of the samples (39 cases) were obtained from patients newly diagnosed. Fourteen were

known for a CMML either in therapeutic abstention (9 cases) or under symptomatic treatment (5 cases). Most patients of the latter group (12/14) were at more of one year after diagnosis. Six patients had received prior chemotherapy or radiotherapy for an independent solid tumour. A normal karyotype was observed in 40 patients (20 MP-CMMLs and 20 MD-CMMLs); a del(20q)(q11q13) was found in 3 patients (2 MP-CMMLs and 1 MD-CMML); a trisomy of a commonly affected chromosome (8, 19, 21) was encountered in 4 MP-CMMLs. One MD-CMML had an 11q inversion, one MP-CMML had a t(10;11)(p12;p15) and one MP-CMML had a t(1;3)(p36;q21). Nucleic acid extraction was done as previously described (Gelsi-Boyer *et al,* 2008).

Array comparative genomic hybridisation (aCGH)

aCGH was done on all samples but two (HD-0397, HD-0715). Some of the results have been published on 38 cases (Gelsi-Boyer *et al,* 2008; Gelsi-Boyer *et al,* 2009). Genomic imbalances were analysed by aCGH using 244K CGH Microarrays (Hu-244A, Agilent Technologies, Massy, France) as previously described (Adélaïde *et al* 2007; Etienne *et al,* 2007). Scanning was done with Agilent Autofocus Dynamic Scanner (G2565BA, Agilent Technologies). Data analysis was done as previously described (Murati *et al,* 2003; Barrett *et al* 2004,) and visualised with CGH Analytics 3.4 software (Agilent Technologies). Extraction data (log_2 ratio) was done with CGH analytics while normalised and filtered log_2 ratios were obtained from « Feature extraction » software (Agilent Technologies). Copy number changes were characterised as reported (Adélaïde *et al,* 2007; Etienne *et al,* 2007).

DNA sequencing

Polymerase chain reaction (PCR) and direct sequencing were done using standard conditions with gene-specific primers designed to amplify coding sequence of *ASXL1* (exon 12), *CBL* (exons 8, 9), *FLT3* (exons 14, 15, 20), *IDH1/2* (exon 4), *JAK2* (exon 14), *K, NRAS* (exons 1, 2), *NPM1* (exon 12), *PTPN11* (exons 3, 11), *RUNX1* (exons 1 to 8), *TET2* (exons 3 to 11) and *WT1* (exons 7, 9) as previously described (Gelsi-Boyer *et al,* 2008; Gelsi-Boyer *et al,* 2009, Kosmider *et al* 2009a, Carbuccia et al, 2010; Kosmider, *et al 2009b*). Primers are described in Gelsi-Boyer *et al*. (2008) and Rocquain *et al*. (2010b). Most PCR amplifications were done in a total volume of 25 µl PCR mix containing at least 10 ng template DNA, Taq buffer, 200 µmol of each deoxynucleotide triphosphate, 20 pmol of each primer and 1 unit of Hot Star Taq (Qiagen). PCR amplification conditions were as follows: 95°C 10 min; 95°C 30 sec, variable temperature 30 sec, 72°C 45 sec for 30 cycles; 72°C 10 min. PCR products were purified using Millipore plate MSNU030. Two microliters of the purified PCR products were used for sequencing using the Big Dye terminator v1.1 kit (Applied Biosystems). After G50 purification, sequences were loaded on an ABI 3130XL automat (Applied Biosystems). The sequence data files were analysed using the SeqScape software and all mutations were confirmed on an independent PCR product.

Statistical Analysis

Clinical and biological factors were taken at the time of sampling whose date corresponds to the search for molecular alterations. The different quantitative biological variables were compared by the Student test (t-test) and prevalence of mutations or alterations detected by karyotype or aCGH by the Chi-square test. Overall survival was defined by the time from the date of diagnosis to the date of

death. Patients still alive were right censored at the date of last contact. “Time-to-AML” was defined by the time from the date of sampling to the date of acute transformation. Patients still alive were right censored at the date of last contact. In time-to-AML analysis, deaths occurring before AML transformation were treated as competing event. To investigate the association between outcome and the different covariates, univariate analysis was done using Log-Rank, Wald, and Gray tests. Cox Proportional Hazard and Fine and Gray models were used in a multivariate approach. Cumulative incidences of AML transformations were estimated by the Prentice method. All statistical tests were two-sided at the 5% level of significance.

Results

aCGH profiles of CMML

We established the aCGH profiles of 51 of the 53 CMML cases. Results are summarized in **Table I**. aCGH revealed alterations that were observed by conventional cytogenetics (9/51) except for 3 patients with balanced translocations (HD-0201, HD-0316, HD-0178), and for case HD-0367 with a del(20)(q11q13) for which aCGH did not show a frank deletion at 20q probably due to the low number of affected cells. For nine cases (17%) aCGH detected rare and limited losses or gains, not visible on the karyotype. They affected very few genes, as previously described (Gelsi-Boyer *et al*, 2008; Adélaïde *et al*, 2010; Rocquain *et al*, 2010a), including some with known tumour suppressor function and leukaemogenic activity (*NF1*, *RB1* and *TET2*). In 70% of cases (36/51) no copy number aberrations were observed.

Mutations in candidate genes are frequent in CMML

We studied coding sequences of 13 genes on the 53 cases (**Table I**). Some results have been previously published (Gelsi-Boyer *et al*, 2008; Gelsi-Boyer *et al*, 2009; Kosmider *et al*, 2009b). In 25 cases (49%) we found 20 frameshift (including 7 times the same p.Gly646Trpfsx12) and 5 nonsense mutations in *ASXL1* exon 12. For three patients (HD-0228, HD-0328, HD-0370), we could demonstrate that the mutation was acquired because the mutation was absent from buccal smear DNA (not shown). *CBL* exon 8 mutations were found in about 10% of cases (5/47); one case (HD-0223) had a homozygous mutation. One case (HD-0367) had an internal tandem duplication of *FLT3*. We found 5 *IDH* mutations in 48 cases (10%); all were in *IDH2* (4 times the same p.Arg140Gln). Seven patients out of the 53 cases (13%) had a *K* or *NRAS* mutation. We previously examined the sequence of exons 3 and 13 of the *PTPN11* gene and mutations were found in two cases (Gelsi-Boyer *et al,* 2008). Twelve out of 53 patients (21%) were mutated for *RUNX1* and 36% of patients were mutated for *TET2*. No mutation was found in *NPM1*, *JAK2* and *WT1*. On the basis of small deletions detected by aCGH and spanning only few genes, we searched for mutations in an additional set of candidate genes: *ASXL2*, *BRAF*, *CBFB, CTNNB1*, *KDM3B*, *KDM6A/UTX, KDM6B, NFIA*, *PYGO1*, *SPI1*, *RAF1*, and *TET3* but failed to find any mutations (unpublished data) except in one patient (HD-0398) for which a mutation in *NFIA* exon 2 was found and previously reported (Bernard *et al,* 2008).

MP- and MD-CMMLs show quantitative differences in molecular alterations

Genomic alterations detected by conventional cytogenetics or aCGH were different in MP- and MD-CMML (**Table I**): 15 out of 31 MP-CMMLs and 4 out of 22

MD-CMMLs showed alterations. MP-CMMLs had more genomic alterations than MD-CMMLs (p=0.049).

We compared the prevalence of the mutated genes in MP and MD-CMML. Nineteen of the 25 *ASXL1* mutations were found in 30 MP-CMMLs *vs* 6 in 22 MD-CMMLs. Mutations in *ASXL1* but not in *RUNX1* or *TET2* were more frequent in MP than in MD-CMMLs (p=0.03) (**Table I**). No difference was observed between the two forms for *CBL*, *FLT3*, *IDH*1/2, *PTPN11*, *RAS*, *RUNX1* or *TET2*. No *RAS* pathway mutation (*RAS* and *PTPN11*) was observed in MD-CMMLs. Mutations in proliferation-associated genes *CBL, FLT3, KRAS, NRAS and PTPN11* were mutually exclusive and taken as a whole significantly associated with MP-CMML (14/123 versus 1/91; p=0.008). Overall, the number of mutations (*ASXL1* and proliferation genes) was higher in MP than in MD-CMMLs (p=0.018).

Altogether, molecular events (mutations and genomic alterations) were more frequent in MP-CMMLs (69/273 events) than in MD-CMMLs (26/172) (p=0.0018).

Correlations between ASXL1 *mutation and clinical and biological features in CMML*

The main clinical and biological features of 51 CMML cases were examined with respect to *ASXL1* mutations (**Table II**). The presence of an *ASXL1* mutation was associated with higher WBC (30 x 10^9 /L *vs* 15 x 10^9 /L) (p=0.006), higher blood (p=0.005) and bone marrow monocytosis (p=0.04) and with lower level of blood haemoglobin (p=0.03). No difference was noted in mean cell volume, blood count of neutrophils and platelets, or bone marrow blasts. In MP-CMMLs, *ASXL1* mutation correlated with a lower level of haemoglobin (p=0.03) and platelet count (p=0.002)

and with a higher monocytosis (p=0.04). In MD-CMMLs, no correlations with *ASXL1* mutation were observed.

Among *ASXL1* mutated cases (25/51), eleven (9 MP and 2 MD) had evolved to acute transformation (**Table II**). For one case (HD-0398) DNA of the acute phase was available; we looked for the *ASXL1* mutation and found the same alteration (not shown). In contrast, no acute transformation was observed in the unmutated cases. In other words, all transformed cases had an *ASXL1* mutation but not all *ASXL1* mutated cases had progressed to AML. *ASXL1* mutation and acute transformation were correlated (p=0.0005). Patient HD-0316 had progressed to acute phase but was not included in the 51 patients since we could not determine the *ASXL1* status because of lack of material at either stage.

Overall survival (median follow-up of 29.5 months) was analysed for the 53 patients. Median overall survival was 27.6 months **(Fig 1A)**. *ASXL1* status could be determined at the time of diagnosis for 51 patients. Kaplan-Meier analysis showed a lower overall survival rate in the *ASXL1* mutated patients (**Fig 1B**). With respect to MP/MD form, only a trend to a better survival of the MD patients was observed (not shown). Within MP-CMML patients, cases mutated for *ASXL1* had a poorer survival than the unmutated cases (not shown). We determined the cumulative incidence of AML (**Fig 1C**) and observed that all the patients who developed AML did so within two years and that *ASXL1* mutation had a strong impact on AML incidence (**Fig 1D**). We did the same analysis for *TET2* mutational status. In contrast to *ASXL1, TET2* had no impact on overall survival (not shown). Given the low number of events for the other genes we did not look for any other clinical or biological correlation.

Univariate analysis of time-to-AML was done on 50 patients using as variables *ASXL1* and *TET2* mutational status and MP/MD form, monocytosis, blast count in

bone marrow, anemia, and CMML1/2 type. The following variables showed significance: *ASXL1* status (p=0.0002; 24-months incidence: 0.48, confidence interval 95: [0.26-0.71]), monocytosis in peripheral blood (p=0.042; 24-months incidence: 0.25, confidence interval 95: [0.12-0.38]; hazard ratio: 1.05, confidence interval 95: [1-1.09]), blast count (p=0.0011; 24-months incidence: 0.25, confidence interval: [0.12-0.38]; hazard ratio: 1.18, confidence interval: [1.07-1.3]) and CMML1/2 (p=0.014; CMML1 24-months incidence: 0.16, confidence interval: [0.04-0.28], hazard ratio: 1; CMML2 24-months incidence: 0.58, confidence interval: [0.23-0.93], hazard ratio: 3.96, confidence interval: [1.34-11.7]). A multivariate analysis of time-to-AML was done using Cox regression model and the same variables. Only the *ASXL1* status retained significant prognostic impact (p<0.0001). Thus, in CMML, *ASXL1* mutation is an unfavourable prognostic factor for overall survival and progression to AML.

Discussion

We established the genomic profiles of a series of 53 CMMLs by using aCGH and sequencing of 13 candidate genes.

ASXL1 *is the most frequently mutated gene in CMML*

In more than two-thirds of cases aCGH profiles did not show any copy number aberrations. In few cases, small copy number aberrations were indicative of genes known (*NF1, RB1, TET2*) or suspected (*SH3KPB1, RAD21*) (Adélaïde *et al*, 2010;

Rocquain *et al*, 2010a) to be involved in leukaemogenesis. MP-CMMLs had more genomic alterations than MD-CMMLs.

We studied 13 candidate genes. We classified these genes into three groups. The first group comprised five known and potential tumour suppressors and transcription factors, the second group six genes associated with kinase activity, signalling pathways and proliferation, and the third group the two *IDH* genes. Hypothetically, CMML could result from a combination of mutation(s) in each of these groups, and perhaps more yet-to-be discovered mutations. Overall, mutations of *ASXL1*, *RUNX1* and *TET2* were prominent in particular in MP-CMMLs but the difference between the two forms was not statistically significant for the three genes taken as a whole (p=0.19). Mutations in these three genes were not mutually exclusive. This is in contrast to what we observed in myelodysplastic syndromes (MDS) and acute myeloid leukaemia where *RUNX1* and *TET2* mutations were mutually exclusive but could each be associated with *ASXL1* mutations (Rocquain *et al*., 2010b). We have no explanation for this observation. *ASXL1* mutations are found in all myeloid neoplasms (Carbuccia *et al,* 2009; Gelsi-Boyer *et al,* 2009; Carbuccia *et al*, 2010; Kosmider *et al,* 2009a; Boultwood *et al*, 2010a; Boultwood *et al*, 2010b; Sugimoto *et al*, 2010; Tefferi, 2010). In the present study *ASXL1* appeared as the most frequently mutated gene in CMML, as it is in MDSs (Boultwood *et al*, 2010a; Rocquain *et al*, 2010b). In MDSs, *ASXL1* mutations are found in high-risk cases.

As previously observed (Gelsi-Boyer *et al,* 2008) mutations in the second group of “proliferation” genes were mutually exclusive. The frequency of mutations of *CBL* was in the range of what was observed recently (Makishima *et al,* 2009). With two exceptions (a *CBL* mutation and an *NF1* deletion detected by aCGH), mutations in these genes were a hallmark of MP-CMML and may explain the proliferative

features of this form. In agreement, it has recently been shown that *JAK2* mutations are associated with MP-CMML (Ricci *et al, 2010*). However, in our series we did not find any *JAK2* mutation. Overall, the number of mutations (*ASXL1* and proliferation genes) was higher in MP-CMML than in MD-CMML. This is a molecular basis to the separation of CMML in MP and MD forms initially defined by the FAB group. However, the equal number of mutations of *RUNX1* and *TET2* in both forms suggests a common mechanism of oncogenesis.

ASXL1 *mutation is associated with poor prognosis and acute transformation of CMML*

The MP and MD classification may have a molecular basis (Gelsi-Boyer *et al,* 2007; this work) but had no significant impact on prognosis in our series. Several studies have similarly found that this classification does not by itself offer enough prognostic information (Germing *et al*, 1998; Nosslinger *et al*, 2001; Gonzalez-Medina *et al*, 2002). We have here shown that, in contrast, *ASXL1* mutation is associated with both poor overall survival and acute transformation. In our series, no unmutated cases had evolved to acute phase whereas the cases that had progressed to acute leukaemia were all mutated (except for one case for which we could not determine the *ASXL1* status). A multivariate analysis of time-to-AML including *ASXL1* mutation and other factors revealed that only *ASXL1* status has significant impact. However, *ASXL1* status was not significant in multivariate analysis of overall survival (not shown), perhaps because of the limited number of cases or the existence of confounding factors such as deaths by other causes. Some mutated cases had not progressed to acute phase. This may be because patients had died before experiencing acute leukaemia. This may have been the case for patients HD-

0230 and HD-0660, whose *ASXL1* mutated CMML progressed from CMML1 to CMML2. For mutated patients still alive it could be a question of time. If this were the case *ASXL1* mutation could be used to predict the risk of progression of CMML to acute leukaemia. In contrast, *TET2* mutations had no impact. A previous study had found prognostic impact of *TET2* mutation but only in CMML1 (Kosmider *et al,* 2009b).

ASXL1 mutation is associated with aggressive forms in other myeloid disorders, including high-risk MDSs, primitive myelofibrosis (Carbuccia *et al*, 2009), secondary acute myeloid leukaemias (Carbuccia *et al*, 2010). If confirmed on a larger series the data would endow *ASXL1* with such a prognostic value that its mutational status may be systematically determined in hospital setting and that the management of patients with mutation may be adapted. It could also be interesting to classify CMMLs studied in clinical trials according to *ASXL1* status.

Author contributions

AM, CA, HZ HF, ZT, MN, MJM, and NV selected the cases, and provided and reviewed the clinical and biological data. JA and MC generated and analyzed the aCGH data. VT, JR, and NC generated and analyzed the sequencing data. BE and PF did the statistical analyses. VGB and DB supervised the study and wrote the manuscript. All authors approved the study and the manuscript.

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Table I. Mutations of candidate genes in a series of CMML.

Case	Sex/Age (years)	Diagnosis	RUNX1 (exons 1-8)	TET2 (exons 3-11)	ASXL1 (exon 12)	NPM1 (exon 12)	WT1 (exons 7, 9)	CBL (exons 8,9)	FLT3 ITD/TKD	JAK2 (V617F)	KRAS (exons 1, 2)	NRAS (exons 1, 2)	PTPN11 (exons 3, 13)	IDH1 (exon 4)	IDH2 (exon 4)	Number of altered genes	Karyotype	aCGH
HD-0176	M/42	MP-CMML1	no	no	no	no	no	no	no	no	no	no	no	no	no	0	46,XY[20]	gain 7p21 (AHR), Xp22 (SH3
HD-0182	F/74	MP-CMML1	no	no	no	no	no	no	no	no	no	p.Gly12Asp	no	no	no	1	45, X, -X?c[20]	loss X
HD-0200	M/71	MP-CMML1	no	no	no	no	no	no	no	no	p.Ala146Val	no	no	no	no	1	46,XY[20]	no CNA
HD-0201	M/87	MP-CMML1	no	no	p.Leu1266HisfsX9	no	no	no	no	no	p.=	p.Ala157Gly	no	no	no	2	46,XY,t(10;11)(p12;p15)[13]/46,XY[7]	no CNA
HD-0223	M/85	MP-CMML1	no	splicing defect	p.Arg1068X	no	no	p.Phe418Ser (hom)	no	no	no	no	nd	no	no	3	46,XY[20]	loss 13q14 (RB1), 15q21, 15q22 gain Xp22
HD-0228	M/70	MP-CMML1	no	p.Trp1198X	p.Thr836LeufsX2 (nc)	no	no	no	no	no	p.Gly12Ser	no	no	no	no	3	46,XY[20]	no CNA
HD-0229	M/87	MP-CMML2	no	p.Gln1191X	no	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0257	F/71	MP-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	p.Arg140Gln	1	46,XX[20]	no CNA
HD-0272	F/79	MP-CMML1	no	p.Arg1452X p.Tyr1560LeufsX18	p.Gly646TrpfsX12	no	no	no	no	no	no	p. Gly13Asp	na	no	no	3	46,XX[20]	no CNA
HD-0273	M/76	MP-CMML1	no	p.Gly1361Ser	p.Lys888GlufsX6	no	no	no	no	no	no	no	na	no	p.Arg140Gln	3	46,XY[20]	no CNA
HD-0316	M/65	MP-CMML1	p.Pro425Leu	na	na	no	na	na	na	no	no	no	p.Asp61Tyr	na	na	2	46,XY[20]	losses 3q22-24 (EPHB1, NEK11,
HD-0318	M/69	MP-CMML1	p.Arg166X	no	p.Gln768X	na	na	na	na	no	no	no	no	na	na	2	46,XY,del(20)(q11q13)[20]	loss 20q11-q13
HD-0320	F/74	MP-CMML2	splicing defect	p.Arg1404X	p.Gly646TrpfsX12	no	no	no	no	no	no	no	p.Ala72Thr	no	no	4	47,XX,+8[20]	tri 8
HD-0321	M/55	MP-CMML2	p.Arg166X	no	p.His630ProfsX66	no	no	na	no	no	no	no	no	no	no	2	46,XY[20]	loss 3p23 (GLB1, CRTA
HD-0322	F/61	MP-CMML1	no	no	no	no	no	no	no	no	no	no	no	no	no	0	46,XX[20]	no CNA
HD-0327	F/72	MP-CMML1	p.Tyr377LeufsX22 3	p.Cys1193Trp	p.Gly646TrpfsX12	no	no	no	no	no	no	p.Gly12Asp	no	no	no	4	47,XX,+8[20]	tri 8, loss 7q11 (CALN1
HD-0366	M/78	MP-CMML1	no	no	p.Ser846GlnfsX5 (nc)	na	na	na	na	no	no	no	no	na	na	1	46,XY[20]	no CNA
HD-0367	F/70	MP-CMML2	no	no	no	no	no	no	ITD	no	no	no	no	no	no	1	46,XX,inv(11)(p15q22)[20]	no CNA
HD-0370	M/70	MP-CMML2	no	no	p.Thr1271LysfsX10 (nc	no	no	no	no	no	no	no	no	no	no	1	46,XY[20]	no CNA
HD-0376	F/65	MP-CMML2	no	no	no	no	no	no	no	no	no	no	no	no	no	0	46,XX,t(1;3)(p36;q21)[20]	no CNA
HD-0397	F/71	MP-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XX[20]	na
HD-0398	M/62	MP-CMML1	no	no	p.Gly646TrpfsX12	no	no	no	no	no	no	no	na	no	no	1	47,XY,+19[17]/46,XY[3]	tri 19
HD-0399	M/74	MP-CMML1	p.Ser141Leu	no	p.Gly646TrpfsX12	no	no	p.Cys396Tyr	no	no	no	no	no	no	no	3	46,XY[20]	no CNA
HD-0404	M/88	MP-CMML2	p.Arg201X	p.Asn1581IlefsX17	p.His630ProfsX66	no	no	no	no	no	no	no	na	no	no	3	47,XY, +21 [20]	tri 21
HD-0485	M/63	MP- CMML 2	p.Arg320X	p.Leu1252Pro	p.Gly646TrpfsX12	no	no	no	no	no	no	no	na	no	no	3	46,XY[20]	no CNA
HD-0627	F/87	MP-CMML1	no	no	p.Arg1068X	no	no	p.Cys404Tyr (hom)	no	no	no	no	na	no	no	2	46,XX,del(20)(q11q13)[6]/46,XX[19]	no CNA
HD-0669	M/88	MP-CMML1	no	no	p.Ala611ArgfsX8	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0671	F/71	MP-CMML1	p.Lys110Arg	no	p.Tyr591X	no	no	no	no	no	no	no	na	no	no	2	47,XX,+19[8]/46,XX[12]	loss 17q11 (NF1), tri 19
HD-0707	M/85	MP-CMML1	no	no	no	no	no	p.Tyr371His	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0715	M/69	MP-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XY[20]	na
HD-0723	M/83	MP-CMML1	no	no	p.1213IlefsX3	no	no	no	no	no	no	p.Gly12Val	na	no	p.Arg140Gln	3	46,XY[20]	no CNA
HD-0178	M/88	MD-CMML1	no	no	no	no	no	no	no	no	no	no	no	no	p.Arg140Gln	1	46,XY,del(20)(q11q13)[20]	loss 13q14 (RB1), 20q11-
HD-0197	M/59	MD-CMML1	p.Arg320X	no	no	na	na	na	na	no	no	no	no	na	na	1	46,XY[20]	no CNA
HD-0206	M/73	MD-CMML2	no	deletion	p.Asp879GlufsX7	no	no	no	no	no	no	no	na	no	p.Arg172Lys	3	46,XY[20]	loss 4q24 (TET2)
HD-0230	M/83	MD-CMML1	no	no	p.His630ProfsX66	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0242	F/82	MD-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XX[25]	no CNA
HD-0254	F/83	MD-CMML2	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XX[20]	loss 17q11 (NF1)
HD-0271	F/82	MD-CMML1	no	no	p.Pro1263GlnfsX17	no	no	no	no	no	no	no	na	no	no	1	46,XX[20]	no CNA
HD-0280	M/78	MD-CMML1	no	p.Ser1189ValfsX37	no	no	no	no	no	no	no	no	na	no	no	1	45,X,-Y[19]/46,XY[1]	loss Y
HD-0328	M/73	MD-CMML1	no	p.Gly355Asp (hom)	p.Gly646TrpfsX12	no	no	p.Cys404Tyr	no	no	no	no	no	no	no	3	46,XY[20]	no CNA
HD-0330	M/76	MD-CMML1	p.Gly50GlnfsX4	na	na	na	na	na	na	no	no	no	no	na	na	1	46,XY[20]	no CNA
HD-0355	M/65	MD-CMML1	no	p.Cys1289Phe	no	no	no	no	no	no	no	no	no	no	no	1	46,XY[20]	no CNA
HD-0372	M/60	MD-CMML1	no	no	no	no	no	no	no	no	no	no	no	no	no	0	46,XY[20]	no CNA
HD-0380	F/82	MD-CMML1	no	p.Gln1414X	no	no	no	no	no	no	no	no	no	no	no	1	46,XX[20]	no CNA
HD-0388	F/71	MD-CMML1	p. Met133Ile	p.Leu1721PhefsX8	no	no	no	no	no	no	no	no	na	no	no	2	46,XX[20]	no CNA
HD-0396	M/70	MD-CMML1	no	p.Ser354X	no	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0638	F/68	MD-CMML1	no	p.Leu1394TrpfsX54	no	no	no	no	no	no	no	no	na	no	no	1	46,XX[20]	no CNA
HD-0660	M/80	MD-CMML1	no	no	p.Arg693X	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0703	M/74	MD-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XY[20]	no CNA
HD-0711	M/79	MD-CMML1	no	p.Gln649X	no	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0712	M/41	MD-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XY[20]	no CNA
HD-0743	M/68	MD-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XY[20]	no CNA
HD-0755	M/46	MD-CMML1	no	p.Arg1359Cys	p.Thr822AsnfsX11	no	no	no	no	no	no	no	na	no	no	2	46,XY[20]	no CNA

Samples are separated according to the white blood cell count: MP-CMML with WBC > $13x10^9$/L and MD-CMML with WBC < $13x10^9$/L.

hom: homozygous; nc : verified as not constitutional

na: non available

Table II. Clinical and biological features of *ASXL1* mutated and unmutated CMML patients.

CMML	Number of patients	*ASXL1* mutated	*ASXL1* unmutated	p value
Sex ratio	51	3.16	1.27	0.23
Age: median (range)	51	74 (46-88)	71 (41-88)	0.39
Leukocyte count: median (range)	51	30 (6-188)	15 (2.8-26.4)	**0.006**
Haemoglobin level (g/dL): median (range)	50	10 (8.1-14.1)	12.5 (7.4-16.2)	**0.03**
MCV: median (range)	35	92 (86-106)	93 (79-101)	0.33
Neutrophil count (G/L): median (range)	41	15 (1.5-41)	2 (0.1-12.9)	0.07
Blood monocyte count (G/L): median (range)	50	4.65 (1-60)	2 (1-46)	**0.005**
Platelets count (G/L): median (range)	50	117.5 (34-420)	208 (39-660)	0.07
Bone marrow blasts (%): median (range)	51	7 (2-18)	6 (1-14)	0.11
Bone marrow monocytes (%): median (range)	50	20 (6-35)	15 (3-45)	**0.04**
MP-CMML	30	19	11	**0.03**
MD-CMML	21	6	15	
No acute transformation	51	14	26	**0.0005**
Acute transformation	51	11	0	
MP-CMML	**Number of patients**	***ASXL1* mutated**	***ASXL1* unmutated**	**p value**
Sex ratio		2.8	0.8	0.25
Age: median (range)	30	74 (55-88)	70.5 (42-87)	0.13
Leukocyte count: median (range)	30	35 (6-188)	17 (15-26.5)	0.08
Haemoglobin level (g/dL): median (range)	29	11 (8.1-12.5)	11.5 (8.5-15.2)	**0.03**
MCV: median (range)	21	92 (80-106)	88.5 (74-101)	0.11
Neutrophil count (G/L): median (range)	26	25 (7-41)	10 (7-12.9)	0.54
Blood monocyte count (G/L): median (range)	30	10 (1-60)	4.5 (1.2-46)	**0.04**
Platelets count (G/L): median (range)	29	118 (34-420)	272 (57-660)	**0.002**
Bone marrow blasts (%): median (range)	30	7 (2-16)	6 (2-14)	0.54
Bone marrow monocytes (%): median (range)	29	25 (6-35)	14 (3-45)	0.16
MD-CMML	**Number of patients**	***ASXL1* mutated**	***ASXL1* unmutated**	**p value**
Sex ratio	21	5	1.8	0.75
Age: median (range)	21	76.5 (46-83)	75 (41-88)	0.9
Leukocyte count: median (range)	21	8.9 (4-12)	7.1 (2.8-12.8)	0.6
Haemoglobin level (g/dL): median (range)	21	12 (8.9-14.1)	14 (7.4-16.2)	0.77
MCV: median (range)	13	89 (86-100)	93.5 (91-101)	0.46
Neutrophil count (G/L): median (range)	19	5 (1.5-7)	7.1 (0.1-7.7)	0.15
Blood monocyte count (G/L): median (range)	21	1.3 (1-4.5)	1.4 (1-2.6)	0.55
Platelets count (G/L): median (range)	21	122 (43-414)	130 (39-399)	0.5
Bone marrow blasts (%): median (range)	21	7 (4-18)	5 (4-13)	0.2
Bone marrow monocytes (%): median (range)	21	16 (10-20)	15 (10-13)	0.83

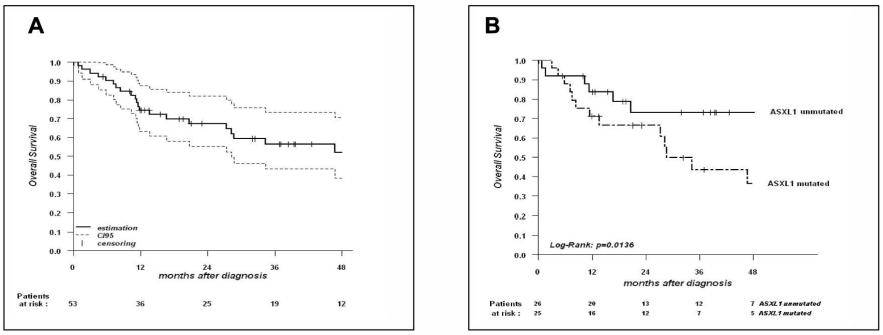
MCV: mean cell volume; In bold: significant p value

Legends to the figure.

Fig 1. Kaplan-Meier overall survival curves for all CMML patients (A) and according to *ASXL1* mutational status (B). The number of patients at risk over time is shown beneath each panel. (C) Cumulative incidence of progression to acute myeloid leukaemia for all patients (C) and according to *ASXL1* mutational status (D).

Table 1. Mutations of candidate genes in a series of CMML.

Case	Sex/Age (years)	Diagnosis	RUNX1 (exons 1-8)	TET2 (exons 3-11)	ASXL1 (exon 12)	NPM1 (exon 12)	WT1 (exons 7, 9)	CBL (exons 8,9)	FLT3 ITD/TKD	JAK2 (V617F)	KRAS (exons 1, 2)	NRAS (exons 1, 2)	PTPN11 (exons 3, 13)	IDH1 (exon 4)	IDH2 (exon 4)	Number of altered genes	Karyotype	aCGH
HD-0176	M/42	MP-CMML1	no	no	no	no	no	no	no	no	no	no	no	no	no	0	46,XY[20]	gain 7p21 (AHR), Xp22 (SH3KBP1)
HD-0182	F/74	MP-CMML1	no	no	no	no	no	no	no	no	no	p.Gly12Asp	no	no	no	1	45, X, -X?c[20]	loss X
HD-0200	M/71	MP-CMML1	no	no	no	no	no	no	no	no	p.Ala146Val	no	no	no	no	1	46,XY[20]	no CNA
HD-0201	M/87	MP-CMML1	no	no	p.Leu1266HisfsX9	no	no	no	no	no	p.=	p.Ala157Gly	no	no	no	2	46,XY,t(10;11)(p12;p15)[13]/46,XY[7]	no CNA
HD-0223	M/85	MP-CMML1	no	splicing defect	p.Arg1068X	no	no	p.Phe418Ser (hom)	no	no	no	no	nd	no	no	3	46,XY[20]	loss 13q14 (RB1), 15q21, 15q22 (DAPK2), gain Xp22
HD-0228	M/70	MP-CMML1	no	p.Trp1198X	p.Thr836LeufsX2 (nc)	no	no	no	no	no	p.Gly12Ser	no	no	no	no	3	46,XY[20]	no CNA
HD-0229	M/87	MP-CMML2	no	p.Gln1191X	no	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0257	F/71	MP-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	p.Arg140Gln	1	46,XX[20]	no CNA
HD-0272	F/79	MP-CMML1	no	p.Arg1452X p.Tyr1560LeufsX18	p.Gly646TrpfsX12	no	no	no	no	no	no	p. Gly13Asp	na	no	no	3	46,XX[20]	no CNA
HD-0273	M/76	MP-CMML1	no	p.Gly1361Ser	p.Lys888GlufsX6	no	no	no	no	no	no	no	na	no	p.Arg140Gln	3	46,XY[20]	no CNA
HD-0316	M/65	MP-CMML1	p.Pro425Leu	na	na	no	na	na	na	no	no	no	p.Asp61Tyr	na	na	2	46,XY[20]	losses 3q22-24 (EPHB1, NEK11, MRAS…)
HD-0318	M/69	MP-CMML1	p.Arg166X	no	p.Gln768X	na	na	na	na	no	no	no	no	na	na	2	46,XY,del(20)(q11q13)[20]	loss 20q11-q13
HD-0320	F/74	MP-CMML2	splicing defect	p.Arg1404X	p.Gly646TrpfsX12	no	no	no	no	no	no	no	p.Ala72Thr	no	no	4	47,XX,+8[20]	tri 8
HD-0321	M/55	MP-CMML2	p.Arg166X	no	p.His630ProfsX66	no	no	na	no	no	no	no	no	no	no	2	46,XY[20]	loss 3p23 (GLB1, CRTAP)
HD-0322	F/61	MP-CMML1	no	no	no	no	no	no	no	no	no	no	no	no	no	0	46,XX[20]	no CNA
HD-0327	F/72	MP-CMML1	p.Tyr377LeufsX223	p.Cys1193Trp	p.Gly646TrpfsX12	no	no	no	no	no	no	p.Gly12Asp	no	no	no	4	47,XX,+8[20]	tri 8, loss 7q11 (CALN1)
HD-0366	M/78	MP-CMML1	no	no	p.Ser846GlnfsX5 (nc)	na	na	na	na	no	no	no	no	na	na	1	46,XY[20]	no CNA
HD-0367	F/70	MP-CMML2	no	no	no	no	no	no	ITD	no	no	no	no	no	no	1	46,XX,inv(11)(p15q22)[20]	no CNA
HD-0370	M/70	MP-CMML2	no	no	p.Thr1271LysfsX10 (nc)	no	no	no	no	no	no	no	no	no	no	1	46,XY[20]	no CNA
HD-0376	F/65	MP-CMML2	no	no	no	no	no	no	no	no	no	no	no	no	no	0	46,XX,t(1;3)(p36;q21)[20]	no CNA
HD-0397	F/71	MP-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XX[20]	na
HD-0398	M/62	MP-CMML1	no	no	p.Gly646TrpfsX12	no	no	no	no	no	no	no	na	no	no	1	47,XY,+19[17]/46,XY[3]	tri 19
HD-0399	M/74	MP-CMML1	p.Ser141Leu	no	p.Gly646TrpfsX12	no	no	p.Cys396Tyr	no	no	no	no	no	no	no	3	46,XY[20]	no CNA
HD-0404	M/88	MP-CMML2	p.Arg201X	p.Asn1581IlefsX17	p.His630ProfsX66	no	no	no	no	no	no	no	na	no	no	3	47,XY,+21 [20]	tri 21
HD-0485	M/63	MP- CMML 2	p.Arg320X	p.Leu1252Pro	p.Gly646TrpfsX12	no	no	no	no	no	no	no	na	no	no	3	46,XY[20]	no CNA
HD-0627	F/87	MP-CMML1	no	no	p.Arg1068X	no	no	p.Cys404Tyr (hom)	no	no	no	no	na	no	no	2	46,XX,del(20)(q11q13)[6]/46,XX[19]	no CNA
HD-0669	M/88	MP-CMML1	no	no	p.Ala611ArgfsX8	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0671	F/71	MP-CMML1	p.Lys110Arg	no	p.Tyr591X	no	no	no	no	no	no	no	na	no	no	2	47,XX,+19[8]/46,XX[12]	loss 17q11 (NF1), tri 19
HD-0707	M/85	MP-CMML1	no	no	no	no	no	p.Tyr371His	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0715	M/69	MP-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XY[20]	na
HD-0723	M/83	MP-CMML1	no	no	p.1213IlefsX3	no	no	no	no	no	no	p.Gly12Val	na	no	p.Arg140Gln	3	46,XY[20]	no CNA
HD-0178	M/88	MD-CMML1	no	no	no	no	no	no	no	no	no	no	no	no	p.Arg140Gln	1	46,XY,del(20)(q11q13)[20]	loss 13q14 (RB1), 20q11-q13
HD-0197	M/59	MD-CMML1	p.Arg320X	no	no	na	na	na	na	no	no	no	no	na	na	1	46,XY[20]	no CNA
HD-0206	M/73	MD-CMML2	no	deletion	p.Asp879GlufsX7	no	no	no	no	no	no	no	na	no	p.Arg172Lys	3	46,XY[20]	loss 4q24 (TET2)
HD-0230	M/83	MD-CMML1	no	no	p.His630ProfsX66	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0242	F/82	MD-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XX[25]	no CNA
HD-0254	F/83	MD-CMML2	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XX[20]	loss 17q11 (NF1)
HD-0271	F/82	MD-CMML1	no	no	p.Pro1263GlnfsX17	no	no	no	no	no	no	no	na	no	no	1	46,XX[20]	no CNA
HD-0280	M/78	MD-CMML1	no	p.Ser1189ValfsX37	no	no	no	no	no	no	no	no	na	no	no	1	45,X,-Y[19]/46,XY[1]	loss Y
HD-0328	M/73	MD-CMML1	no	p.Gly355Asp (hom)	p.Gly646TrpfsX12	no	no	p.Cys404Tyr	no	no	no	no	no	no	no	3	46,XY[20]	no CNA
HD-0330	M/76	MD-CMML1	p.Gly50GlnfsX4	na	na	na	na	na	na	no	no	no	no	na	na	1	46,XY[20]	no CNA
HD-0355	M/65	MD-CMML1	no	p.Cys1289Phe	no	no	no	no	no	no	no	no	no	no	no	1	46,XY[20]	no CNA
HD-0372	M/60	MD-CMML1	no	no	no	no	no	no	no	no	no	no	no	no	no	0	46,XY[20]	no CNA
HD-0380	F/82	MD-CMML1	no	p.Gln1414X	no	no	no	no	no	no	no	no	no	no	no	1	46,XX[20]	no CNA
HD-0388	F/71	MD-CMML1	p. Met133Ile	p.Leu1721PhefsX8	no	no	no	no	no	no	no	no	na	no	no	2	46,XX[20]	no CNA
HD-0396	M/70	MD-CMML1	no	p.Ser354X	no	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0638	F/68	MD-CMML1	no	p.Leu1394TrpfsX54	no	no	no	no	no	no	no	no	na	no	no	1	46,XX[20]	no CNA
HD-0660	M/80	MD-CMML1	no	no	p.Arg693X	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0703	M/74	MD-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XY[20]	no CNA
HD-0711	M/79	MD-CMML1	no	p.Gln649X	no	no	no	no	no	no	no	no	na	no	no	1	46,XY[20]	no CNA
HD-0712	M/41	MD-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XY[20]	no CNA
HD-0743	M/68	MD-CMML1	no	no	no	no	no	no	no	no	no	no	na	no	no	0	46,XY[20]	no CNA



Kaplan-Meier overall survival curves for all CMML patients (A) and according to ASXL1 mutational status (B). The number of patients at risk over time is shown beneath each panel. (C) Cumulative incidence of progression to acute myeloid leukaemia for all patients (C) and according to ASXL1 mutational status (D).
529x396mm (96 x 96 DPI)

Supplementary Table I. Clinical and biological features of a series of CMML.

Patient	Sex/Age (years)	Diagnosis (WHO)	Antecedent of chemotherapy or radiotherapy	Organomegaly	Peripheral blood		Bone marrow		Acute transformation	Treatment at sampling
					WBC (G/L)	Monocytes (G/L)	Blasts (%)	Monocytes (%)		
MP-CMML										
HD-0176	M/42	CMML 1	no	no	17.3	1.2	2	12	no	none
HD-0182	F/74	CMML 1	no	no	16.0	1.9	3	3	no	none
HD-0200	M/71	CMML 1	no	no	22	7	8	32	no	TA
HD-0201	M/86	CMML 1	nd	splenomegaly	116.8	40	7	nd	yes	none
HD-0223	M/85	CMML 1	no	no	27.9	4.9	2	18	no	none
HD-0228	M/70	CMML 1	no	splenomegaly hepatomegaly	32	5	5	12	no	TA
HD-0229	M/87	CMML 2	yes	no	16	3.2	12	22	no	none
HD-0257	F/71	CMML 1	no	no	16.3	2	5	17	no	EPO
HD-0272	F/79	CMML 1	no	no	10	3	3	7	no	hydrea
HD-0273	M/76	CMML 2	no	no	32.4	15	9	23	no	TA
HD-0316	M/65	CMML 2	no	no	37	5.7	15	12	no	none
HD-0318	M/69	CMML 1	yes	splenomegaly hepatomegaly	30	1	3	6	yes	none
HD-0320	F/74	CMML 2	no	no	43.5	14.5	15	16	yes	none
HD-0321	M/55	CMML 2	no	no	55	14.8	15	35	yes	none
HD-0322	F/61	CMML 1	no	no	38	3.5	3	6	no	hydrea
HD-0327	F/72	CMML 1	no	no	188	43	9	27	yes	none
HD-0366	M/78	CMML 1	no	no	13.2	4.6	3	33	no	TA
HD-0367	F/70	CMML 2	yes	no	64	46	14	40	no	none
HD-0370	M/70	CMML 2	no	splenomegaly	25.4	2.5	18	10	yes	TA
HD-376	F/65	CMML 2	yes	no	18	2.9	11	14	no	transfusions
HD-0397	F/72	CMML 1	no	no	26.5	4.7	6	45	no	none
HD-0398	M/59	CMML 1	no	splenomegaly	36	3	6	20	yes	hydrea
HD-0399	M/74	CMML 1	no	splenomegaly. microadenomegaly	6	2	6	30	no	hydrea + EPO
HD-0404	M/89	CMML 1	no	no	35	12	16	34	no	none
HD-0485	M/63	CMML 2	no	no	14.7	4.4	12	22	no	none
HD-0627	F/86	CMML 1	no	splenomegaly	41.7	10	5	28	no	none
HD-0669	M/88	CMML 1	no	no	28.4	6.8	8	37	no	TA
HD-0671	F/71	CMML 2	no	no	35.9	4.7	15	30	yes	none
HD-0707	M/85	CMML 1	no	no	11.8	2.25	4	28	no	hydrea
HD-0715	M/69	CMML 1	no	no	15	1.4	7	6	no	none
HD-0723	M/83	CMML 1	no	no	17.9	2.87	5	12	yes	TA
MD-CMML										
HD-0178	M/88	CMML 1	no	no	6.9	1.5	7	22	no	none
HD-0197	M/59	CMML 1	no	hepatomegaly	11.4	2.6	6	23	no	none
HD-0206	M/73	CMML 2	no	no	8.8	1.2	18	13	yes	none
HD-0230	M/86	CMML 1	no ?	no	10.4	1.78	8	20	no	none
HD-0242	F/82	CMML 1	no	no	6.9	1.9	5	10	no	none
HD-0254	F/83	CMML 2	no	no	9.1	1	13	15	no	none
HD-0271	F/82	CMML 1	no	no	9	1.35	6	18	no	none
HD-0280	M/79	CMML 1	no	no	7.1	1.3	7	18	no	TA
HD-0328	M/73	CMML 1	no	no	7.4	4.5	4	20	no	none
HD-0330	M/76	CMML 1	no	hepatomegaly	5.1	1.79	7	16	no	none
HD-0355	M/65	CMML 1	yes	no	4	1	7	12	no	none
HD-0372	M/60	CMML 1	no	no	12	1.1	4	10	no	none
HD-0380	M/82	CMML 1	no	splenomegaly polyadenomegaly	5.4	1.1	4	10	no	none
HD-0388	F/71	CMML 1	no	no	7.1	1.15	6	22	no	none
HD-0396	M/79	CMML 1	no	nd	10.3	2	4	11	no	none
HD-0638	F/68	CMML 1	no	no	5.1	1.38	8	18	no	none
HD-0660	M/80	CMML 1	no	microadenomegaly	6.1	1.7	5	15	no	TA
HD-0703	M/74	CMML 1	no	no	12.8	1.42	1	4	no	none
HD-0711	M/78	CMML 1	no	no	9.74	1.35	3	19	no	transfusions
HD-0712	M/41	CMML 1	no	no	9.8	1	3	6	no	none
HD-0743	M/68	CMML 1	no	no	2.8	2	7	19	no	none
HD-0755	M/46	CMML 1	yes	no	9.8	2.4	4	12	yes	none

MP-CMML : myeloproliferative form of chronic myelomonocytic leukaemia defined by a leukocytosis superior to 13x 10^9 /L

MD-CMML : myelodysplastic form of chronic myelomonocytic leukaemia defined by a leukocytosis inferior to 13x 10^9 /L

nd : no data

TA : therapeutic abstention

EPO: erythropoietin