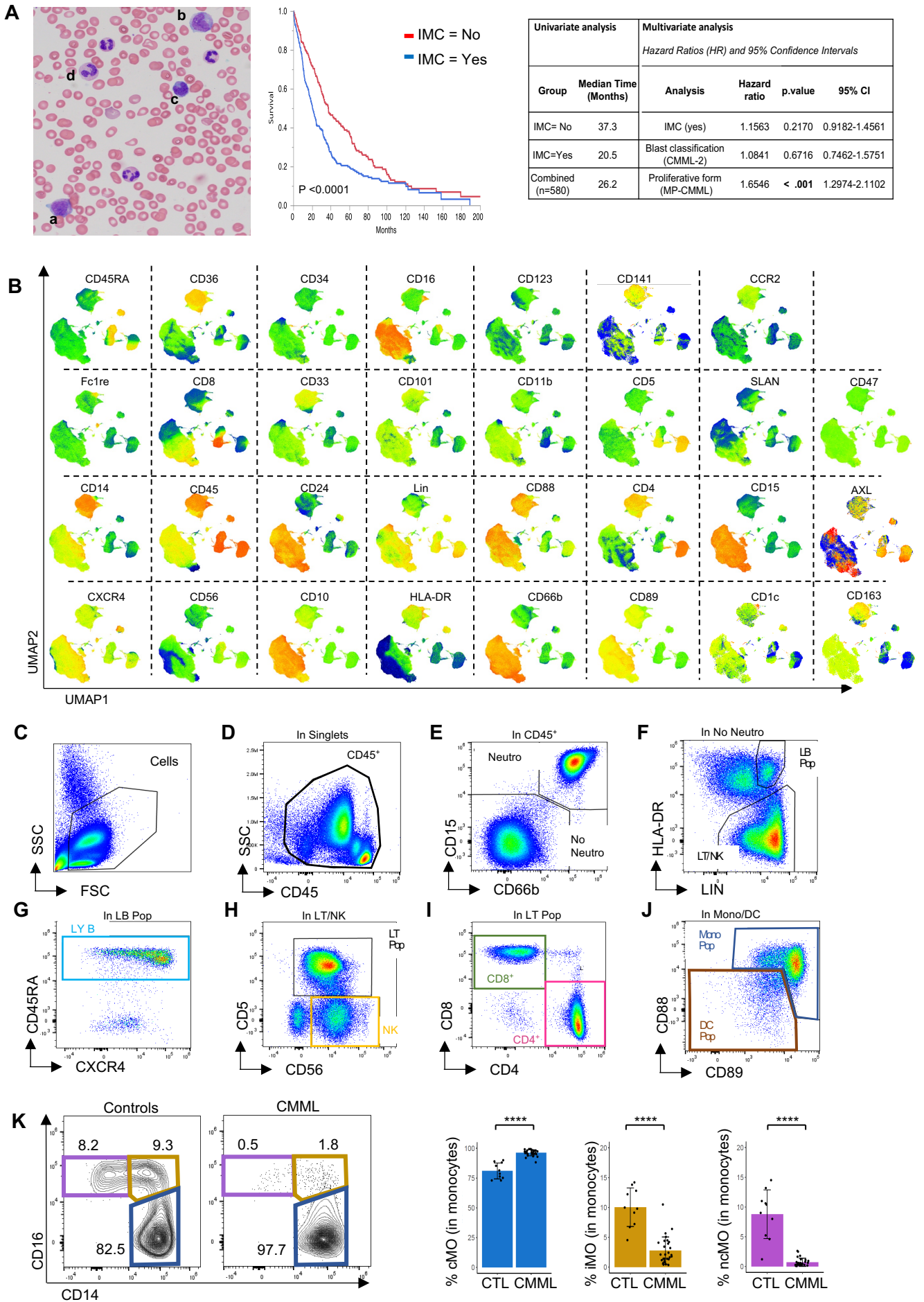


## Deschamps et al. Supplemental Figure 1

**Supplemental Figure 1. Spectral flow analysis of peripheral blood cells.** **A.** Left, representative blood smear of a CMML patient with immature myeloid cells (IMC) (a) myelocyte, (b and c) atypical monocyte, (d) band form. Middle, overall survival of 580 CMML patients using IMC cutoff (Yes,  $\geq 1\%$  of white blood cell, WBC). Right, univariate analysis of IMC impact on overall survival; N=580 patients (IMC < 1%, N=229; IMC  $\geq 1\%$  WBC, N=351) and multivariate analysis built on 466 patients with available informations on IMC fraction, bone marrow blast cell count (CMML-2) and WBC count (MP-CMML). **B.** Cell surface marker expression in the non-supervised UMAP analysis of 37 samples (controls, N=10; CMML, N=27); **C-J.** Gating strategy for cell subset analysis in CD45<sup>+</sup> cell population. Debris and doublets were discarded by gating on “Cells” (**C**), “Singlets” and “Singlets bis” gates (not shown). Remaining red cells were excluded and CD45<sup>+</sup> cells were selected on a dot plot of CD45 vs SSC (**D**). CD15<sup>+</sup>, CD66b<sup>+</sup> granulocytes were isolated in a “Neutro” gate (**E**) and separated into mature CD15<sup>+</sup>, CD16<sup>+</sup> and immature CD15<sup>+</sup>, CD16<sup>-</sup> neutrophils (not shown). Other hematopoietic cells in a “No Neutro” gate, CD15<sup>-</sup>, CD66b<sup>-</sup> (**E**) include lymphoid populations, roughly isolated as expressing CD3 or CD19 or CD7 or NKG2D (LIN<sup>+</sup>) using LIN vs HLA-DR dot plot, separating B-cells (LIN<sup>+</sup>, HLA-DR<sup>+</sup>) from NK / T cells (LIN<sup>+</sup>, HLA-DR<sup>-</sup>) (**F**). B-cells were further detected on a CXCR4 vs CD45RA dot plot (**G**), NK cells on a CD56 vs CD5 dot plot (**H**) and T-cells as CD5<sup>+</sup> cells, CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes (**I**). With this exclusion gating strategy, remaining cells could be considered as monocytes and dendritic cells and monocyte subsets “Mono Pop” were separated from Dendritic cells “DC Pop” on a CD89 vs CD88 dot plot (**J**). **K.** Monocyte subsets in the “Mono pop” gate were separated on a CD14 vs CD16 dot plot into classical (cMO in blue), intermediate (iMO, in yellow) and non-classical monocytes (ncMO, in purple)(left panels) and the fraction of each subset was calculated in controls (CTL, N=10) and CMML (N=27) samples (right panels).

# Deschamps et al. Supplemental Figure 1

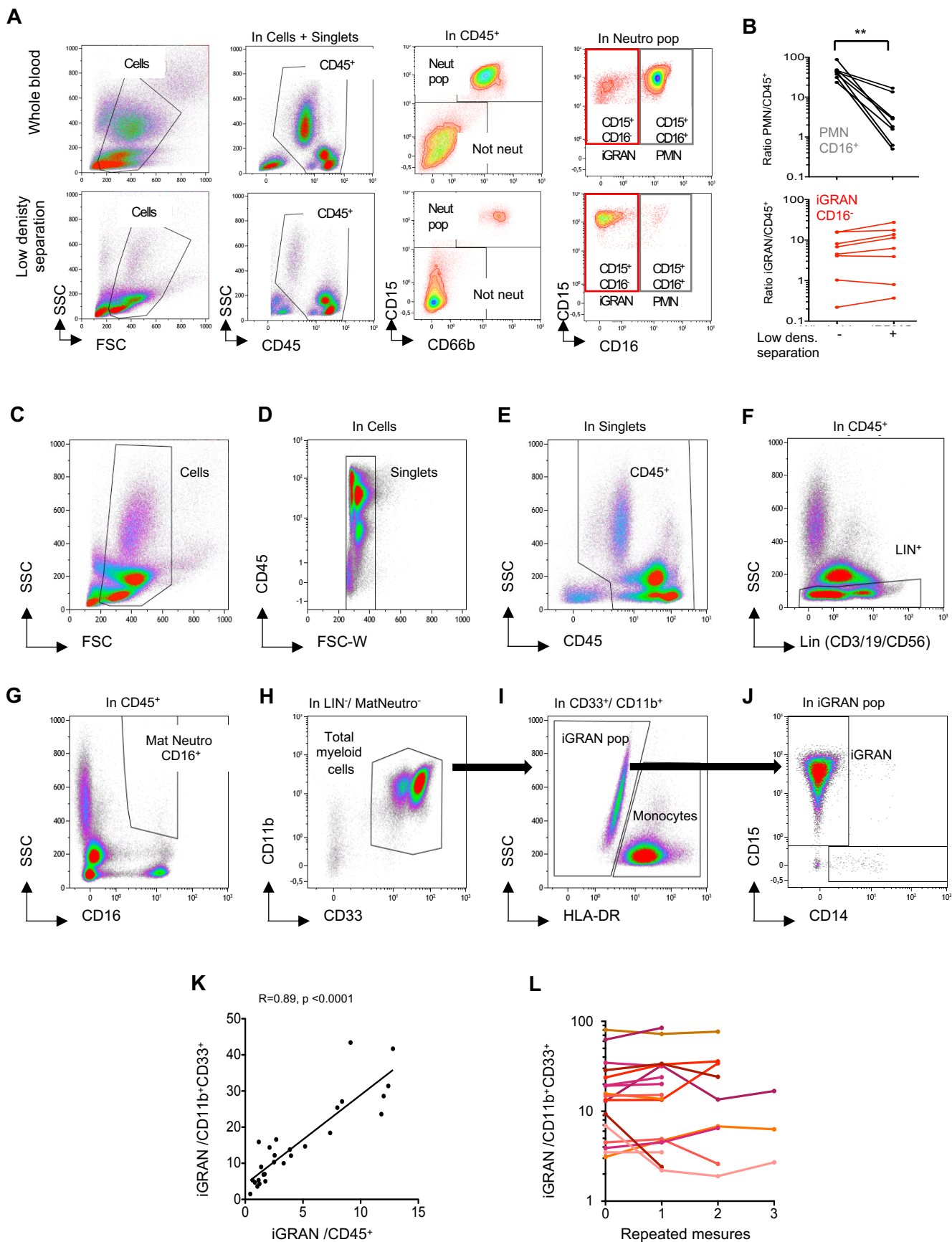


## Deschamps et al. Supplemental Figure 2

### Supplemental Figure 2. Conventional flow detection of iGRAN in CMML peripheral blood.

**A.** Representative flow plots showing the presence of iGRANs in the peripheral blood before (whole blood) and after low-density separation. **B.** Ratio of PMN (CD15<sup>+</sup>, CD16<sup>+</sup> cells, upper panel, in grey) or iGRAN (CD15<sup>+</sup>, CD16<sup>-</sup>, lower panel, in red) to CD45<sup>+</sup> cells before and after low density separation. N=8. Student paired test. **C-J.** Step by step gating strategy to quantify iGRAN fraction after low-density separation of peripheral blood cells; forward (FSC) and side scatter (SSC-A) are used to discard debris and dead cells (**C**) and doublets (**D**); CD45<sup>+</sup> cells were selected on a CD45/ SSC plot (**E**); lymphoid cells were selected with a pool of Lin antibodies (anti-CD3, CD-19 and CD-56 in the same fluorescence channel, LIN<sup>+</sup>) (**F**); remaining mature neutrophils were selected on a CD16/ SSC plot (**G**); total myeloid cells were selected as CD33<sup>+</sup>, CD11b<sup>+</sup> cells in the “LIN<sup>-</sup> / Mature neutro” population (**H**); among the CD33<sup>+</sup>, CD11b<sup>+</sup> myeloid cells, monocytes were identified as HLA-DR<sup>+</sup> cells on a HLA-DR vs SSC plot (**I**); iGRANs were identified by CD15<sup>+</sup> expression in the HLA-DR<sup>-</sup> population (**J**). The absolute number of iGRAN was deducted from the ratio of monocyte count in WBC count to the number of cells in the “monocyte gate”, applied to the number of cells in the “iGRAN gate”. **K.** Spearman correlation between iGRAN fraction calculated in CD11b<sup>+</sup>, CD33<sup>+</sup> and in CD45<sup>+</sup> populations. **L.** iGRAN fraction was serially measured, up to three times over a period of one year, in CMML patients (N= 17).

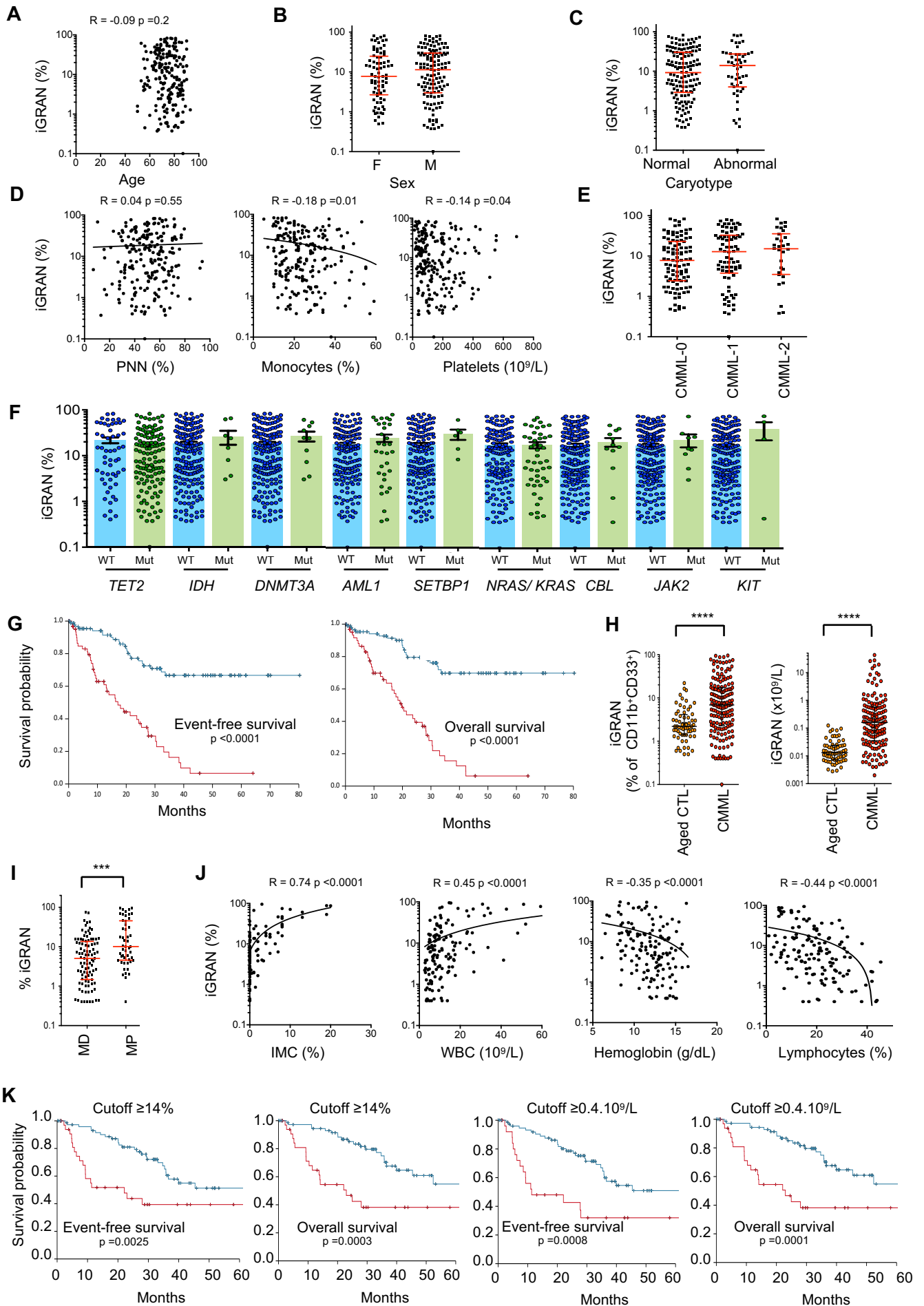
# Deschamps et al. Supplemental Figure 2



## Deschamps et al. Supplemental Figure 3

**Supplemental Figure 3. Relationship between iGRAN fraction, CMML features and patient outcome in the learning and the validation cohorts. A-G. Learning cohort. A.** Spearman correlation between iGRAN fraction and patient age. **B.** iGRAN fraction in female (F) and male (M) CMML patients. **C.** iGRAN fraction according to the presence or absence of cytogenetic abnormalities. **D.** Spearman correlation between iGRAN fraction and mature neutrophil fraction (PNN, left panel), monocyte fraction (middle panel) and platelet count (right panel). **E.** iGRAN fraction according to WHO 2016 CMML subtypes. **F.** iGRAN fraction according to the wildtype (WT) or mutated (Mut) status of indicated genes. **G.** Event-free survival (left) and overall survival (right) of CMML patients with high ( $\geq 0.4 \times 10^9/L$ , N=63 in red) and low ( $< 0.4 \times 10^9/L$ , N=91 in blue) number of circulating iGRANs, log-rank test. **H-K. Validation cohort. H.** iGRAN fraction in CD11b<sup>+</sup>CD33<sup>+</sup> population (left panel) and iGRAN absolute number (right panel) measured by flow cytometry in the peripheral blood of a validation cohort of CMML patients (N=160) compared to age-matched controls (N=64). Mann-Whitney test. **I.** iGRAN fraction in dysplastic (MD) and proliferative (MP) CMML subtypes. Mann-Whitney test. **J.** Spearman correlation between iGRAN fraction and immature myeloid cell (IMC) fraction, white blood cell count (WBC), hemoglobin level and lymphocyte fraction in the peripheral blood of CMML patients. **K.** Event-free survival and overall survival of CMML patients included in the validation cohort, using the cutoffs values calculated within the learning cohort. CMML patients with high ( $\geq 14\%$ , N=34, in red) vs low ( $< 14\%$ , N=76, in blue) iGRAN fraction (left); CMML patients with high ( $\geq 0.4 \times 10^9/L$ , N=27 in red) vs low ( $< 0.4 \times 10^9/L$ , N=79 in blue) number of circulating iGRANs (right), log-rank test.

# Deschamps et al. Supplemental Figure 3

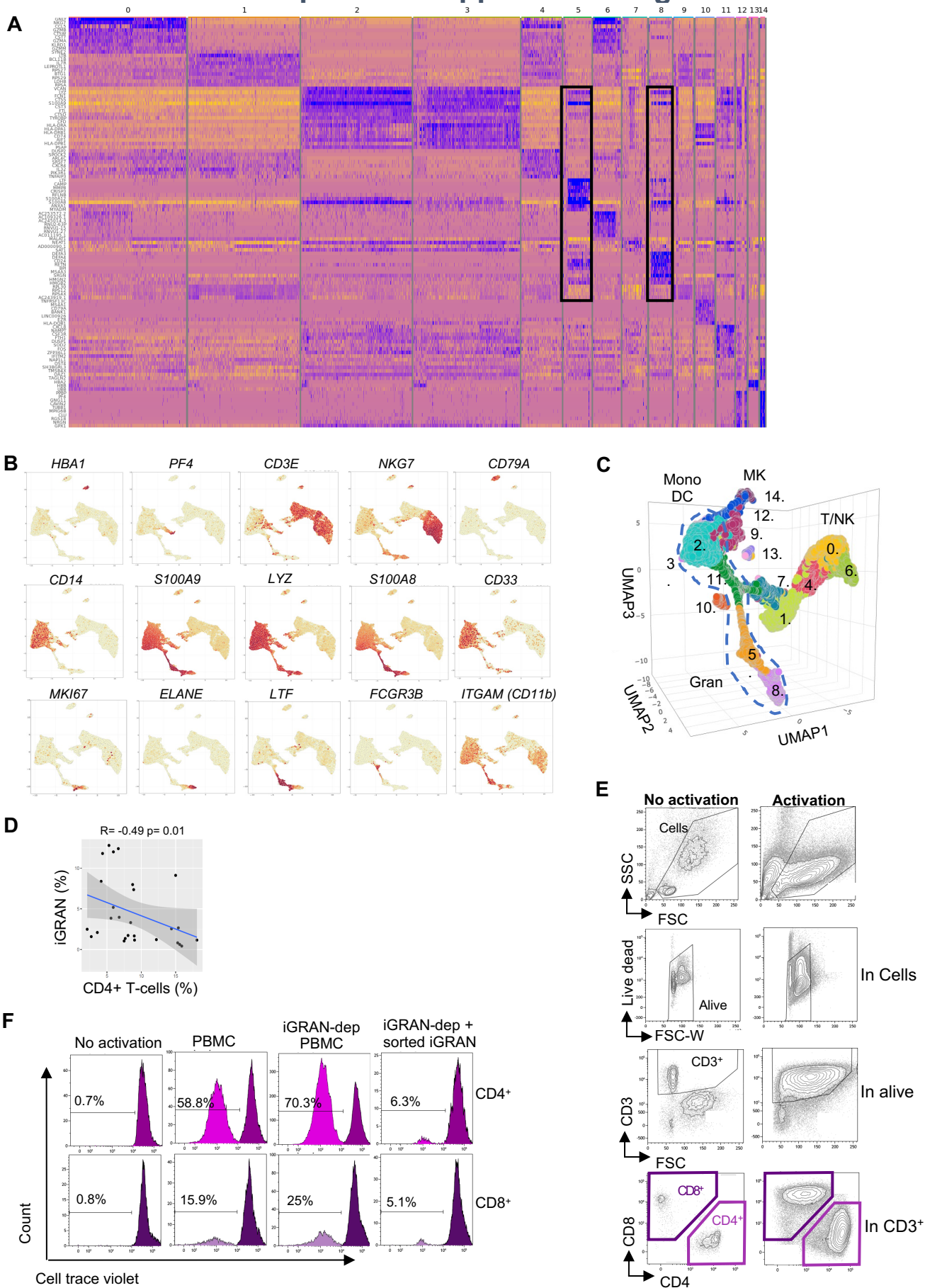




## Deschamps et al. Supplemental Figure 4

**Supplemental Figure 4. Molecular and functional characterization of iGRANs.** **A.** Heatmap displaying the scaled expression patterns of top marker genes within each cluster shown on Figure 3B. Scales indicate the intensity of expression. **B.** Expression level of indicated genes (low expression in yellow to high expression in red) in clusters identified on the UMAP shown on Figure 3B. **C.** Unsupervised clustering of cells in 3D (resolution 0.5 showing 15 main clusters). The dashed lined indicates ITGAM<sup>+</sup> myeloid population selected to calculate iGRAN fraction. **D.** Spearman correlation between iGRAN and CD4<sup>+</sup> T-cell fractions quantified by spectral flow cytometry. **E.** Proliferation assay performed in non-activated and anti-CD3/anti-CD28 activated T-cells; Forward (FSC) and side scatter (SSC-A) were used to discard debris. Dead cells and doublets were excluded using a live dead blue staining before selecting CD3<sup>+</sup> cells using FSC/ CD3 dot plot, then separating CD4<sup>+</sup> and CD8<sup>+</sup> T-cells. **F.** Examples of dot plots showing T cell proliferation measured by cell trace violet dilution in conditions described on Figure 3G.

# Deschamps et al. Supplemental Figure 4

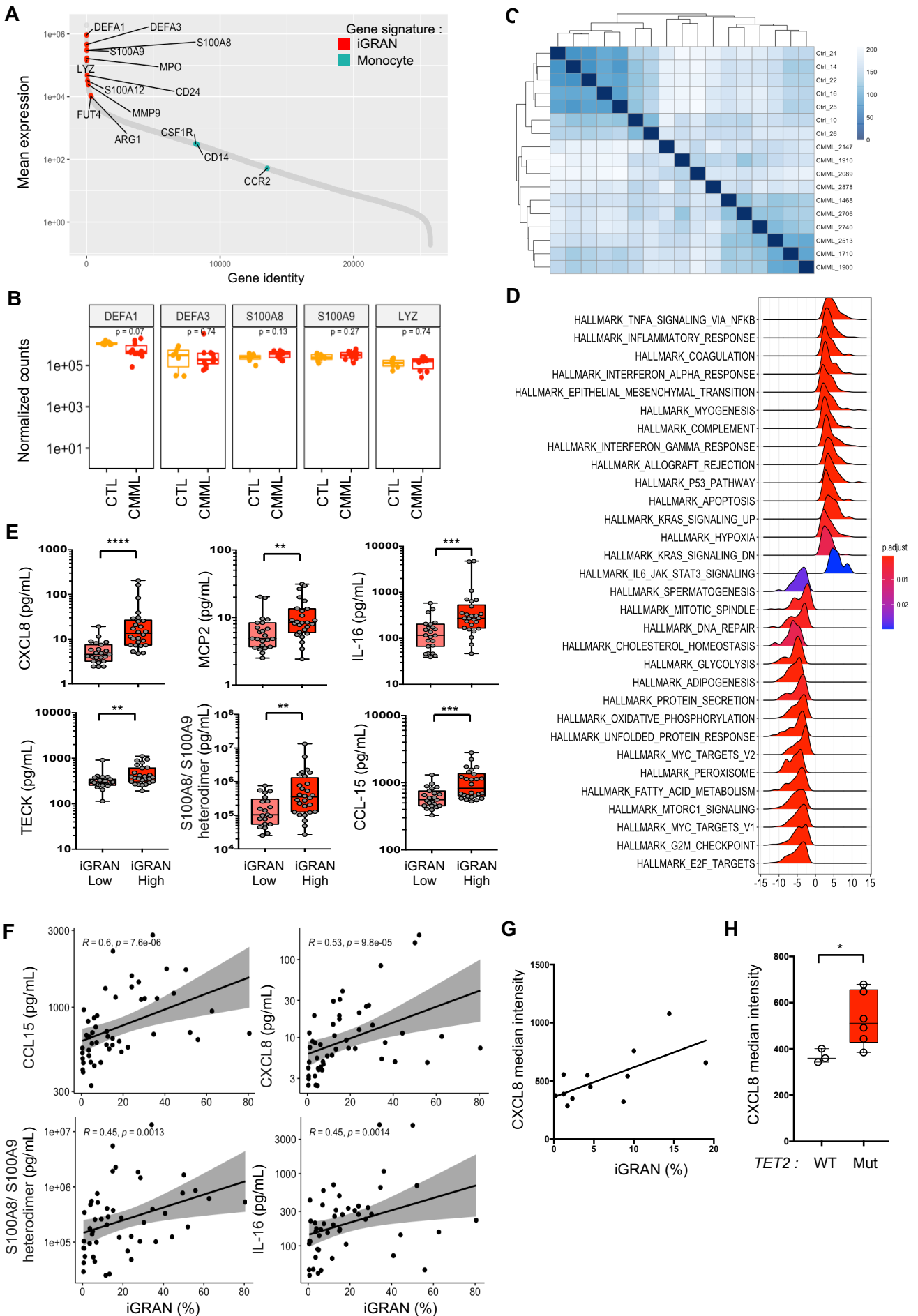




## Deschamps et al. Supplemental Figure 5

**Supplemental Figure 5. Sorted iGRAN RNA sequencing and cytokines associated to their accumulation in CMML patient peripheral blood.** iGRANs were sorted from healthy donor (cytapheresis, N=7) and CMML patient (N=10) peripheral blood. **A.** Mean expression of genes (using DESeq2 normalized counts) in the 17 samples sorted by decreasing order. Examples of genes highly expressed by iGRANs are in red and those highly expressed by monocytes in blue. **B.** Expression of genes (normalized counts) typically identified in iGRANs collected from controls (CTL) and CMML patients. Mann-Whitney test. **C.** Heatmap of sample-to-sample distances based on the rlog transformed counts. **D.** Ridgeplot representing gene set enrichment analysis (GSEA) of pathways distinguishing CMML from control iGRANs ( $p < 0.05$ ). **E.** Circulating levels of indicated cytokines in 23 iGRAN-Low and 26 iGRAN-High (cutoff  $\geq 14\%$ ) CMML patients. Mann-Whitney test. **F.** Spearman correlation between iGRAN fraction in myeloid cells and plasma level of indicated cytokines. **G.** Spearman correlation between iGRAN fraction in myeloid cells and CXCL8 median fluorescence intensity in neutrophils (as shown in Figure 5F). **H.** CXCL8 median fluorescence intensity measured by flow cytometry in iGRAN from 9 CMML patients including 3 wildtype (WT) and 6 TET2 mutated cases (Mut).

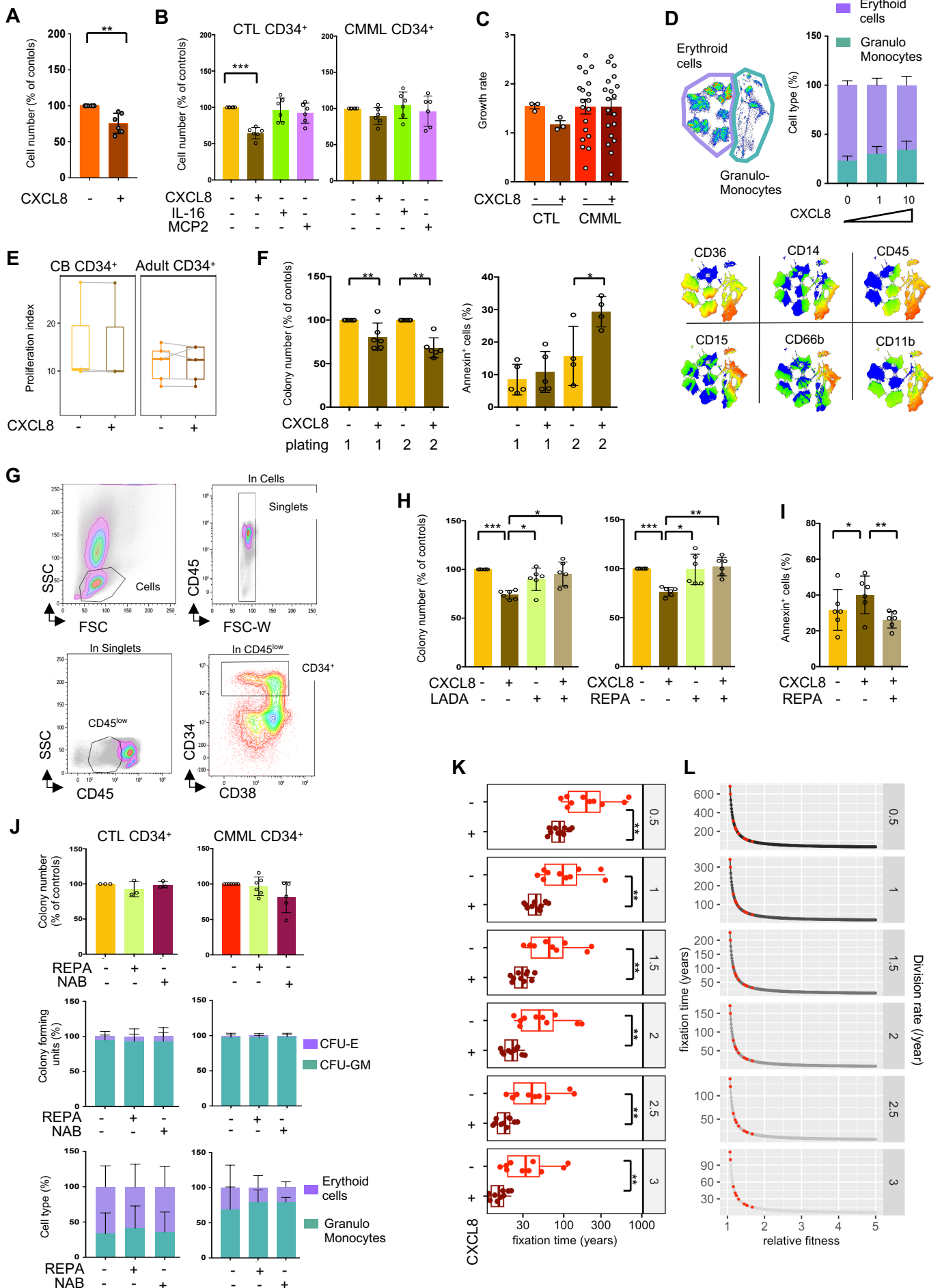
# Deschamps et al. Supplemental Figure 5



## Deschamps et al. Supplemental Figure 6

**Supplemental Figure 6. CXCL8 blockade restores CD34<sup>+</sup> wildtype growth.** **A.** Cell output of healthy donor bone marrow CD34<sup>+</sup> in liquid culture for 3 days in the presence of 10 ng/mL CXCL8; ratio to untreated samples; mean  $\pm$  SD, N=6. Paired t test. **B.** Cell output of WT or CMML CD34<sup>+</sup> cells in liquid culture for 3 days in the absence or presence of 10 ng/mL CXCL8, IL-16 or MCP2; ratio to untreated samples; mean  $\pm$  SD, N=6 per group. Mann-Whitney test. **C.** Growth rate (LN(number of cells at day 3 / number of cells at day 0)) of healthy donor bone marrow CD34<sup>+</sup> (N=3) or CMML CD34<sup>+</sup> cells (N=19) in liquid culture for 3 days in the absence or presence of 10 ng/mL CXCL8. **D.** Non-supervised UMAP of spectral flow cytometry analysis of cells generated from healthy donor bone marrow CD34<sup>+</sup> in methylcellulose at day 14 in the absence or presence of CXCL8 (10 ng/mL, N=5 independent experiments). Left: UMAP analysis separating CD45<sup>-</sup>, CD11b<sup>-</sup>, CD36<sup>+</sup> erythroid cells from CD45<sup>+</sup>, CD11b<sup>+</sup>, CD14<sup>+</sup> monocytes and CD45<sup>+</sup>, CD11b<sup>+</sup>, CD15<sup>+</sup>, CD66b<sup>+</sup> granulocytes; right : fraction of erythroid or granulo-monocytic cells, lower panel: projection of indicated markers on UMAP. **E.** Proliferation index measuring the number of divisions of CD34<sup>+</sup> cells collected from WT donors (cord blood, CB, N=3 or adult bone marrows, Adult, N=4), in presence or absence of CXCL8. **F.** Total colony output of healthy donor CD34<sup>+</sup> culture in methylcellulose in presence or absence of CXCL8 (10 ng/mL) during serial replatings (plating 1 or 2, left panel). Percentage of dead cells measured by flow cytometry (Annexin-V<sup>+</sup>/ propidium iodide <sup>-</sup>/<sup>+</sup> ; right panel) (N=6). Paired t test. **G.** Gating strategy to explore CXCR1 and CXCR2 expression at the surface of CD34<sup>+</sup> cells. **H.** Total colony output of healthy donor CD34<sup>+</sup> cell culture in methylcellulose in presence or absence of CXCL8 (10 ng/mL) and a CXCR1/2 inhibitor [left panel, ladarixin (LADA, 10  $\mu$ M); right panel, reparixin (REPA, 10  $\mu$ M)]; ratio related to untreated samples; Mean  $\pm$  SD; N=6. **I.** Percentage of dead cells measured by flow cytometry (Annexin-V<sup>+</sup>/ propidium iodide <sup>-</sup>/<sup>+</sup>) during serial replating 2 in presence or absence of CXCL8 and reparixin (REPA, N=6). **J.** Impact of Reparixin (REPA) or Blocking antibody (NAB) on CD34<sup>+</sup> cells from healthy donors (CTL, left panels) and CMML (right panels) in methylcellulose. Upper panels : total colony output for CD34<sup>+</sup> cells from healthy donors (cord blood, CB, N=3) or CMML (N=5); ratio related to untreated samples. Middle panels : fractions of CFU-GM and CFU-E represented together (CB, N=3; CMML, N=5) . Lower panels: Spectral flow cytometry analysis of cells collected from culture in methylcellulose (CB, N=2; CMML N=4). **K-L.** Fixation time (in years) estimated using a Moran birth-death process, assuming 100,000 HSCs and testing 6 different HSC division rates (from 0.5 to 3) **J.** Fixation time estimated from our growth rate data (panel C), for 10 CMML samples with a growth rate superior to the mean of CTRL growth rate, faceted by division rate, in presence (maroon) or absence (red) of CXCL8. **K.** Fixation time as a function of relative fitness, for relative fitnesses from 1.07 to 5 at steps of 0.01, faceted by division rate. Red points: the 10 CMML samples of panel J, in absence of CXCL8.

# Deschamps et al. Supplemental Figure 6



**Supplementary Table 1.** Clinical and laboratory characteristics of CMML patients stratified by the presence or absence of circulating immature myeloid cells (IMCs) in the peripheral blood at diagnosis; continuous variables, median (range); dichotomized variables (N, %). ALC: absolute lymphocyte count; AMC: absolute monocyte count; ANC: absolute neutrophil count; WBC: white blood cell count; PB: peripheral blood; BM: bone marrow. Mann-Whitney test or Kruskal-Wallis test. The bold values represent p values that are statistically significant; p < 0.05.

	All patients	CMML with IMCs	CMML w/o IMCs	P value
<b>Number</b>	580	351	229	
<b>Age in years; median (range)</b>	71 (18 - 95)	70 (18 - 95)	72 (20 - 95)	0.06
<b>Males; N (%)</b>	392 (68)	235 (67)	157 (69)	0.68
<b>Hemoglobin, g/dL; median (range)</b>	10.7 (4.3 - 17)	10.5 (4.3 - 16.9)	11.3 (6.4 - 17)	<b>0.005</b>
<b>WBC x10<sup>9</sup>/L; median (range)</b>	12.9 (1.3- 264.8)	18.4 (1.8-185.7)	7.9 (1.3- 264.8)	<b>&lt;0.0001</b>
<b>ANC x 10<sup>9</sup>/L; median (range)</b>	6.2 (0 - 151)	8.9 (0.06 - 151)	3.8 (0 - 142.9)	<b>&lt;0.0001</b>
<b>AMC x 10<sup>9</sup>/L; median (range)</b>	2.7 (0 - 84)	3.3 (0.1 - 84)	1.7 (0 - 24.6)	<b>&lt;0.0001</b>
<b>ALC x 10<sup>9</sup>/L; median (range)</b>	1.9 (0 - 22)	2.15 (0 - 14.5)	1.6 (0.2 - 22)	<b>&lt;0.0001</b>
<b>Platelets x 10<sup>9</sup>/L; median (range)</b>	101 (7 - 1473)	97 (7 - 1473)	109 (12 - 1277)	0.17
<b>Abnormal cytogenetics; N (%)</b>	178/551 (32)	114/330 (35)	64/221 (29)	0.16
<b>Proliferative MP-CMML; N (%)</b>	288 (50)	231 (66)	57 (25)	<b>&lt;0.0001</b>
<b>Dysplastic MD-CMML; N (%)</b>	292 (50)	120 (34)	172 (75)	
<b>CMML-0; N (%)</b>	328 (57)	172 (49)	156 (68)	<b>&lt;0.0001</b>
<b>CMML-1; N (%)</b>	147 (25)	103 (29)	44 (19)	
<b>CMML-2; N (%)</b>	104 (18)	75 (21)	29 (13)	
<b>Next generation sequencing analysis; N</b>	342	201	141	
<b>TET2</b>	180 (53)	104 (52)	76 (55)	0.59
<b>DNMT3A</b>	16 (5)	9 (4)	7 (5)	0.83
<b>IDH1</b>	6 (2)	5 (3)	1 (1)	0.19
<b>IDH2</b>	20 (6)	12 (6)	8 (6)	0.9
<b>ASXL1</b>	200 (54)	130 (59)	70 (46)	<b>0.01</b>
<b>EZH2</b>	13 (4)	10 (5)	3 (2)	0.16
<b>RUNX1</b>	33 (10)	17 (8)	16 (11)	0.37
<b>BCOR</b>	3 (1)	2 (1)	1 (1)	0.77
<b>SF3B1</b>	17 (5)	7 (3)	10 (7)	0.13
<b>SRSF2</b>	158 (46)	99 (49)	59 (42)	0.19
<b>U2AF1</b>	25 (7)	11 (5)	14 (10)	0.12
<b>ZRSR2</b>	11 (3)	7 (3)	4 (3)	0.73
<b>JAK2 V617F</b>	30 (9)	17 (8)	13 (9)	0.8
<b>MPL</b>	1 (0.3)	1 (0.5)	0 (0)	0.3
<b>CBL</b>	50 (15)	33 (16)	17 (12)	0.25
<b>KRAS</b>	19 (6)	10 (5)	9 (6)	0.57
<b>NRAS</b>	51 (15)	32 (16)	19 (13)	0.53
<b>PTPN11</b>	10 (3)	7 (3)	3 (2)	0.45
<b>CSF3R</b>	3 (1)	3 (1.5)	0 (0)	0.07
<b>C-KIT</b>	11 (3)	4 (2)	7 (5)	0.12
<b>FLT3TKD</b>	9 (3)	6 (3)	3 (2)	0.62
<b>NPM1</b>	1 (0.3)	0 (0)	1 (1)	0.18
<b>Tp53</b>	10 (3)	7 (3)	3 (2)	0.45
<b>SETBP1</b>	40 (12)	25 (12)	15 (11)	0.6
<b>Leukemic transformation; N (%)</b>	116 (20)	73 (21)	43 (19)	0.55
<b>Deaths; N (%)</b>	398 (69)	245 (70)	153 (67)	0.44

**Supplementary Table 2.** List and references of antibodies used in indicated assays.

REAGENT	COLOR	CAT. NUMBER	CLONE	SOURCE
<b>Antibodies for Spectral flow cytometry</b>				
CD24	BB700	566525	ML5	BD Biosciences
CD1c	BUV563	748724	F10/21A3	BD Biosciences
CD141	BV421	565321	1A4	BD Biosciences
CD101	BV605	747548	V7.1	BD Biosciences
CD163	BUV737	741863	GHI/61	BD Biosciences
CD34	BUV661	749902	581	BD Biosciences
CD36	BUV496	750114	CLB-IVC7	BD Biosciences
CD5	BV750	747108	UCHT2	BD Biosciences
CD45RA	BUV395	740315	5H9	BD Biosciences
CD15	PE-Dazzle 594	562463	HI98	BD Biosciences
CD16	BUV805	748850	3G8	BD Biosciences
FcER1a	eFluor 450	48-5899-41	AER-37 (CRA1)	ThermoFisher
NKG2D	PerCP-eFluor 710	46-5878-41	1D11	ThermoFisher
CD3	PerCP-eFluor 710	46-0037-41	OKT3	ThermoFisher
CD7	PerCP-eFluor 710	46-0078-41	4H9	ThermoFisher
CD19	PerCP-eFluor 710	46-0198-42	SJ25C1	ThermoFisher
CD123	superbright436	62-1239-42	6H6	ThermoFisher
SLAN	FITC	130-117-371	DD1	Miltenyibiotech
AXL	APC	FAB154A	#108724	R&D
CD66b	Alexa Fluor 647	305109	G10F5	Biolegend
CD89	APC-Fire 750	354115	A59	Biolegend
CCR2	BV785	357233	K036C2	Biolegend
CD11b	BV650	101239	M1/70	Biolegend
CD33	BV570	303417	WM53	Biolegend
HLA-DR	PE-Fire810			Biolegend
CD14	Sparkle blue 550	367147	63D3	Biolegend
CD56	PE-Fire 700	392427	NCAM	Biolegend
CXCR4	PE-CY5	306508	12G5	Biolegend
CD45	Percp	304026	HI30	Biolegend
CD10	PE-CY7	312214	HI10A	Biolegend
CD8	BV510	344732	SK1	Biolegend
CD88	PE	344303	C5aR	Biolegend
CD47	BV711	563761	B6H12	BD Biosciences
CD4	CfluorYG584		SK3	CYTEK
<b>Antibodies for conventional flow cytometry</b>				
CD24	BUV395	563818	ML5	BD Biosciences
CD15	PE-Dazzle 594	562463	HI98	BD Biosciences
CD16	APC-H7	560195	3G8	BD Biosciences
CD3	APC	555342	HIT3a	BD Biosciences
CD19	APC	55415	SJ25C1	BD Biosciences
CD66b	FITC	555724	G10F5	BD Biosciences
CD11b	Percp-CY5.5	301328	ICRF44	Biolegend
CD33	PE	555450	WM53	BD Biosciences
HLA-DR	BV421	562804	G46-6	Biolegend
CD14	PE-CY7	A22331	RMO52	Beckman Coulter
CD56	APC	IM2474	N901	Beckman Coulter
CD45	BV510	304036	HI30	Biolegend
<b>Antibodies for semi-solid culture analysis</b>				
CD163	BUV737			
CD15	PE-Dazzle 594	562463	HI98	BD Biosciences
CD66b	Alexa Fluor 647	305109	G10F5	Biolegend
CD11b	BUV805			Biolegend
CD45	BV510	304036	HI30	Biolegend
CD14	Sparkle blue 550	367147	63D3	Biolegend
CD36	BUV496	750114	CLB-IVC7	BD Biosciences
GPA	PE			
<b>Antibodies for proliferation assays</b>				
CD3	BUV738		UCHT1	BD Biosciences
CD4	APC		OKT4	Biolegend
CD8	BV786		RPA-T8	BD Biosciences
<b>Antibodies for bone marrow CD34<sup>+</sup> analysis</b>				
CD45	APC-H7	561863	HI30	BD Biosciences
CD34	PE-CY7	560710		BD Biosciences
CD38	eFluor 450	48-0388-42		ThermoFisher
CXCR1 CD181	BV650	749071		BD Biosciences
CXCR2 CD182	BUV737	743422		BD Biosciences



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***Antibodies for intracellular staining***

CD19	APC	55415	SJ25C1	BD Biosciences
CD56	APC	IM2474	N901	Beckman Coulter
CD66b	FITC	555724	G10F5	BD Biosciences
CD3	BUV737	612750	UCHT1	BD Biosciences
CD16	Pacific blue	B36292	3G8	Beckman Coulter
CD45	BV510	304036	HI30	Biolegend
CD14	BV605	564054	M5E2	BD Biosciences
CD15	AF-700	301920	HI98	Biolegend

**Supplementary Table 3.** Clinical and laboratory characteristics of CMML patients and age-matched controls tested by spectral or by conventional flow cytometry (learning cohort and validation cohorts). Continuous variables, median (range); dichotomized variables (N, %). ALC: absolute lymphocyte count; AMC: absolute monocyte count; ANC: absolute neutrophil count; WBC: white blood cell count; GFM: groupe francophone des myelodysplasies. Mann-Whitney test or Kruskal-Wallis test. The bold values represent p values that are statistically significant;  $p < 0.05$ . No information available for young donors.

	<i>Spectral flow cytometry</i>			<i>Conventional flow cytometry</i>				
	<i>Cohort</i>			<i>Aged controls</i>	<i>Learning cohort</i>		<i>Validation cohort</i>	
	<i>Aged controls</i>	<i>CMML</i>	<i>p value</i>		<i>CMML</i>	<i>p value</i>	<i>CMML</i>	<i>p value</i>
<b>Number</b>	<b>10</b>	<b>27</b>		<b>64</b>	<b>209</b>		<b>160</b>	
<b>Age in years</b>	71.5 (65-79)	76.0 (60-92)	0.17	74.0 (65-94)	75.0 (50-93)	0.95	75.0 (42-95)	0.91
<b>Males; N (%)</b>	4 (40%)	16 (60%)		28 (46%)	132 (63%)		92(58%)	
<b>Hemoglobin, g/dL</b>	13.9 (13.1-15.8)	12.4 (8.4-16.2)	0.01	13.4 (10.7-16.8)	11.9 (6.4-17.2)	<b>&lt;0.0001</b>	12.0 (6.1-16.5)	<b>&lt;0.0001</b>
<b>WBC x 10<sup>9</sup>/L</b>	5.5 (4.4-7.7)	7.2 (3.1-19.9)	0.085	6.9 (4.5-12.5)	10.7 (2.7-141.9)	<b>&lt;0.0001</b>	9.55 (2.6-76)	<b>&lt;0.0001</b>
<b>ANC x 10<sup>9</sup>/L</b>	3.1 (2.3-5.8)	3.2 (1.2-9.4)	0.64	4.3 (1.9-7.0)	5.4 (0.5-65.9)	<b>0.0042</b>	5.2 (0.1-68.8)	0.034
<b>Neutrophils (%)</b>	57.3 (40.0-75.3)	50.3 (29.9-77.0)	0.129	61.5 (36.0-78.0)	51.0 (7.0-93.8)	<b>&lt;0.0001</b>	52.7 (2.6-92)	0.0002
<b>AMC x 10<sup>9</sup>/L</b>	0.4 (0.3-0.6)	1.65 (1-6.6)	<b>&lt;0.0001</b>	0.6 (0.3-0.9)	2.22 (1-59.7)	<b>&lt;0.0001</b>	1.85 (0.5-28.8)	<b>&lt;0.0001</b>
<b>Monocytes (%)</b>	7.5 (6.0-11.0)	28 (12.8-42.0)	<b>&lt;0.0001</b>	8.7 (3.7-17.8)	23.0 (10.0-64.0)	<b>&lt;0.0001</b>	21.4 (10.0-57.7)	<b>&lt;0.0001</b>
<b>ALC x 10<sup>9</sup>/L</b>	1.5 (1.1-3.1)	1.4 (0.4-3.8)	0.27	1.9 (1.2-2.9)	1.9 (0.3-10)	0.6	1.7 (0.4-12)	0.4
<b>Lymphocytes (%)</b>	29.0 (15.6-43.8)	22.2 (3.1-39.5)	0.006	27 (16-51)	18 (1.4-50)	<b>&lt;0.0001</b>	19 (1-63)	<b>&lt;0.0001</b>
<b>Platelets x 10<sup>9</sup>/L</b>	227 (183-369)	127 (25-1097)	0.0009	234 (152-431)	111 (12-688)	<b>&lt;0.0001</b>	140 (13-1090)	<b>&lt;0.0001</b>
<b>Abnormal karyotype/tested; N (%)</b>	NA	2 / 18 (11%)		NA	46 / 190 (24%)		22 / 104 (21%)	
<b>Proliferative; N (%)</b>	NA	23 (85%)		NA	83 (40%)		48 (34%)	
<b>Dysplastic; N (%)</b>	NA	4 (15%)		NA	126 (60%)		94 (66%)	
<b>CMML-0; N (%)</b>	NA	15 (55%)		NA	104 (49%)		62 (43%)	
<b>CMML-1; N (%)</b>	NA	10 (38%)		NA	77 (36.5%)		64 (44%)	
<b>CMML-2; N (%)</b>	NA	2 (7%)		NA	31 (14.5%)		19 (13.0%)	
<b>Classical monocytes. (% total monocytes)</b>	NA	97.5% (94.4-99.5)		NA	96.9%. (69-99.5)		96.7%. (54-99.6)	
<b>GFM prognosis model, N</b>		27 CMML tested			180 CMML tested		140 CMML tested	
<b>GFM, low; N (%)</b>	NA	21 (78%)		NA	93 (52%)		107 (76%)	
<b>GFM, intermed; N (%)</b>	NA	4 (15%)		NA	59 (33%)		23 (17%)	
<b>GFM, high; N (%)</b>	NA	2 (7%)		NA	28 (15%)		10 (7%)	
<b>NGS analysis; N</b>		27 CMML tested			180 CMML tested		121 CMML tested	
<b>TET2 mutated N (%)</b>	NA	23 (85%)		NA	120 (67%)		89 (73%)	
<b>SRSF2 mutated N (%)</b>	NA	15 (55%)		NA	64 (36%)		45 (37%)	
<b>ASXL1 mutated N (%)</b>	NA	11 (41%)		NA	48 (27%)		44 (36%)	
<b>NRAS mutated N (%)</b>	NA	2 (7%)		NA	22 (12%)		13 (11%)	
<b>KRAS mutated N (%)</b>	NA	3 (11%)		NA	21 (12%)		16 (13%)	
<b>CBL mutated N (%)</b>	NA	5 (19%)		NA	14 (8%)		14 (11%)	
<b>AML1 mutated N (%)</b>	NA	2 (7%)		NA	33 (18%)		17 (14%)	

**Supplementary Table 4.** Correlation between iGRNs ( $\times 10^9/L$ ) and clinical and biological disease parameters. Mann-Whitney test or Kruskal-Wallis test.

<b>Parameters</b>	<b>Number</b>	<b>Median [95%CI]</b>	<b>Significance</b>
<b>A - Categorical variables</b>			
<b>Sex</b>			NS
<i>Females</i>	77	0.2 [0.05-2.06]	
<i>Males</i>	132	0.22 [0.04-2.05]	
<b>WHO CMML subtype 2016</b>			<b>0.019</b>
<i>CMML-0</i>	101	0.15 [0.04-0.76]	
<i>CMML-1</i>	77	0.28 [0.06-2.58]	
<i>CMML-2</i>	31	0.91 [0.07-5.79]	
<b>FAB CMML subtype</b>			<b>P&lt;0001</b>
<i>Dysplastic</i>	126	0.07 [0.03-0.21]	
<i>Proliferative</i>	83	2.23 [0.62-7.54]	
<b>ASXL1 mutation</b>			<b>P&lt;0001</b>
<i>Absent</i>	150	0.13 [0.04-0.71]	
<i>Present</i>	53	2.49 [0.28-5.64]	
<b>TET2 mutation</b>			NS
<i>Absent</i>	64	0.18 [0.04-3.42]	
<i>Present</i>	140	0.21 [0.05-1.45]	
<b>SRSF2 mutation</b>			NS
<i>Absent</i>	121	0.17 [0.04-1.07]	
<i>Present</i>	73	0.36 [0.07-2.88]	
<b>AML1 mutation</b>			NS
<i>Absent</i>	168	0.19 [0.04-1.75]	
<i>Present</i>	35	0.38 [0.07-5.01]	
<b>NRAS mutation</b>			<b>0.005</b>
<i>Absent</i>	179	0.17 [0.04-1.51]	
<i>Present</i>	24	1.31 [0.25-5.57]	
<b>KRAS mutation</b>			NS
<i>Absent</i>	177	0.23 [0.05-2.15]	
<i>Present</i>	26	0.07 [0.03-0.58]	
<b>CBL mutation</b>			NS
<i>Absent</i>	187	0.19 [0.04-1.72]	
<i>Present</i>	16	1.52 [0.1-4.65]	
<b>GFM prognostic score</b>			<b>P&lt;0001</b>
<i>Low</i>	116	0.07 [0.03-0.21]	
<i>Int</i>	62	1.12 [0.21-3.03]	
<i>High</i>	30	5.32 [2.35-12.06]	
<b>CPSS risk stratification</b>			<b>P&lt;0001</b>
<i>Low</i>	75	0.07 [0.03-0.19]	
<i>Int-1</i>	55	0.58 [0.10-2.15]	
<i>Int-2</i>	56	1.19 [0.24-9.45]	
<i>High</i>	5	2.19 [1.12-5.79]	
<b>CPSS-M risk stratification</b>			<b>P&lt;0001</b>
<i>Low</i>	34	0.07 [0.03-0.19]	
<i>Int-1</i>	46	0.08 [0.04-0.25]	
<i>Int-2</i>	51	0.61 [0.1-2.75]	
<i>High</i>	49	2.49 [0.34-7.55]	
<b>B - Continuous variables</b>			
<b>Age</b>	<b>Number</b>	<b>Spearman correlation</b>	<b>Significance</b>
<i>Age</i>	209	-0.05	NS
<i>Hemoglobin, g/dL</i>	209	-0.3	<b>P&lt;0001</b>
<i>Platelets, <math>\times 10^9/L</math></i>	209	-0.15	<b>0.02</b>
<i>WBC count, <math>\times 10^9/L</math></i>	209	0.71	<b>P&lt;0001</b>
<i>Neutrophils (%)</i>	209	-0.0093	NS
<i>Monocytes (%)</i>	209	-0.03	NS
<i>Lymphocytes (%)</i>	208	-0.47	<b>P&lt;0001</b>
<i>IMC (%)</i>	187	0.73	<b>P&lt;0001</b>

**Supplementary Table 5.** Correlation between iGRANs (expressed in fraction or absolute number  $\times 10^9/L$ ) and overall survival or event-free survival (EFS, defined as the time between diagnosis and AML transformation, death, or last follow-up) using Cox models. Multivariate model were built after adjusting for potential confounders (Age, WBC  $> 15 \times 10^9/L$ , hemoglobin  $< 10g/L$ , platelets  $< 100 \times 10^9/L$ , ASXL1 mutations). The proportional hazard hypothesis was verified by visual display of the cumulative sums of martingale residuals.

<b>Analysis with continuous data</b>	<b>Hazard ratio [95%CI] (univariate model)</b>	<b>P – value</b>	<b>Hazard ratio [95%CI] (multivariate model)</b>	<b>P – value</b>
<b>Overall survival (OS)</b>				
<i>iGRAN (%)</i>	1.029 [1.019-1.038]	<0.0001	1.014 [1.00-1.026]	0.0115
<i>iGRAN (<math>10^9/L</math>)</i>	1.104 [1.074-1.135]	<0.0001	1.059 [1.02-1.099]	0.0028
<b>Event-free survival (EFS)</b>				
<i>iGRAN (%)</i>	1.028 [1.019-1.037]	<0.0001	1.016 [1.00-1.026]	0.0049
<i>iGRAN (<math>10^9/L</math>)</i>	1.103 [1.074-1.132]	<0.0001	1.067 [1.03-1.105]	0.0003
<b>Analysis with an iGRAN cutpoint</b>				
	<b>Hazard ratio [95%CI] (univariate model)</b>	<b>P – value</b>	<b>Hazard ratio [95%CI] (multivariate model)</b>	<b>P – value</b>
<b>Overall survival (OS)</b>				
<i>iGRAN (14%)</i>	5.93 [3.364-10.454]	<0.0001	3.678 [1.850-7.305]	0.0002
<i>iGRAN (<math>0.4 \times 10^9/L</math>)</i>	5.49 [3.183-9.470]	<0.0001	3.115 [1.482-6.548]	0.0027
<b>Event-free survival (EFS)</b>				
<i>iGRAN (14%)</i>	5.10 [2.993-8.684]	<0.0001	3.003 [1.592-5.663]	0.0007
<i>iGRAN (<math>0.4 \times 10^9/L</math>)</i>	4.79 [2.857-8.032]	<0.0001	2.579 [1.292-5.149]	0.0003

**Supplementary Table 6.** Variant allele frequency (VAF) detected by Whole-exome sequencing (WES) performed in monocytes, T cells and iGRANs sorted from 14 CMML blood samples. All mutations were found in both iGRANs and monocytes, but not or at low VAF in T lymphocytes.

	Mutated gene	Variant allele frequency		
		T Lymphocytes	Monocytes	iGRANs
<b>WES4</b>	<i>ROCK2</i>	2.83%	58.4%	50%
	<i>TMEM247</i>	9.44%	23.44%	23%
	<i>FILIP1</i>	5.14%	50%	43.88%
	<i>COL1A2</i>	8.2%	54.55%	48.39%
	<i>FCN2</i>	4.67%	42.65%	44%
	<i>KRAS</i>	4.46%	36.88%	33.76%
	<i>MGAT4C</i>	9.68%	44.19%	35.59%
	<i>EPB42</i>	6.43%	51.27%	48.6%
	<i>GMEB2</i>	6.58%	49.46%	50.36%
	<i>C6orf223</i>	6.67%	42.22%	32,07%
<b>WES10</b>	<i>NSD1</i>	0.61%	20.43%	26.97%
	<i>GIMAP1</i>	1.55%	19.8%	33.16%
	<i>RIOX1</i>	0%	14.81%	21.95%
	<i>ATXN3</i>	9.09%	42.25%	27.96%
	<i>TULP2</i>	0%	13.56%	26.12%
	<i>TET2</i>	14.76%	27.94%	28.11%
	<i>NRAS</i>	3%	5%	31%
	<i>PTPN11</i>	5%	8%	10%
<b>WES8</b>	<i>IFNG</i>	3.9%	50.9%	86%
	<i>MGAT4D</i>	15.8%	80%	39%
	<i>DDX20</i>	0%	34.4%	25.9%
	<i>TET2</i>	26.5%	43.7%	49.2%
	<i>TET2</i>	57.1%	55.7%	50%
	<i>NRAS</i>	23.2%	35%	42%
	<i>ASXL1</i>	28.4%	47.8%	41%
	<i>PIR</i>	35%	54%	49%
	<i>GRM4</i>	18.75%	49%	38%
	<i>ZPLD1</i>	28.6%	47%	46%
<i>LAMB2</i>	26.2%	51%	54%	
<b>WES3</b>	<i>ZRANB2</i>	1.65%	32.61%	14.57%
	<i>NRAS</i>	4.75%	16.98%	27.55%
	<i>NBEAL1</i>	8.86%	42.86%	40%
	<i>MAST4</i>	3.15%	51.92%	40.72%
	<i>TNFRSF10A</i>	6.36%	49.3%	43.88%
	<i>C8orf34</i>	6.97%	43.48%	38.06%
	<i>ZFHX4</i>	0%	50%	36%
	<i>KIAA2026</i>	8.22%	45.1%	37.5%
	<i>PRSS3</i>	7.68%	18.09%	16.39%
	<i>KRAS</i>	0.46%	25.42%	12.9%
	<i>PTPN11</i>	6.47%	48.54%	47.62%
	<i>LDHD</i>	1.35%	28.18%	12.73%
	<i>SRSF2</i>	8.08%	42.31%	47.97%
	<i>APLP1</i>	8.06%	48.39%	42.31%
	<i>ATP1A3</i>	6.67%	48.85%	48.08%
<i>TET2</i>	25%	51%	54%	

<b>WES5</b>	<i>ADAMTS20</i>	20.6%	45.8%	49.4%
	<i>ACCS</i>	19.7%	51.9%	41.4%
	<i>TUSC1</i>	15.8%	56.1%	57.9%
	<i>COL5A3</i>	20.8%	50%	51.9%
	<i>APPL1</i>	26.4%	58.1%	46.4%
	<i>TET2</i>	12.2%	48.3%	46.1%
	<i>TET2</i>	20.8%	40.4%	46.4%
	<i>SRSF2</i>	26.22%	48.2%	42.3%
	<i>MRGPRE</i>	11.5%	40.5%	45.4%
	<i>ADAMTSL2</i>	10%	60%	40.2%
	<i>E2F3</i>	19.6%	44.8%	46.7%
	<i>MEGF6</i>	28.3%	35%	51.2%
	<i>ASXL1</i>	20%	23%	23.8%
	<i>NF1</i>	10.8%	48.7%	28%
	<i>CBL</i>	42%	98%	99%
	<i>FOS</i>	27.8%	48.5%	43%
<i>UPF3A</i>	20%	40.5%	36.8%	
<b>WES2</b>	<i>C1orf185</i>	3.03%	38.46%	46.43%
	<i>NRAS</i>	8.66%	47.46%	39.39%
	<i>FMN2</i>	4.45%	11.11%	11.11%
	<i>ARSI</i>	8.74%	49.74%	47.21%
	<i>PSMB5</i>	9.26%	42.02%	47.54%
	<i>DNAH9</i>	4.71%	24.36%	20.5%
	<i>NF1</i>	7.02%	29.23%	18.78%
	<i>SETBP1</i>	7.31%	46.39%	37.57%
	<i>ASXL1</i>	9.52%	27.66%	27.19%
<b>WES1</b>	<i>MPL</i>	2.35%	10.76%	25.25%
	<i>KANK4</i>	7.69%	60.49%	48.19%
	<i>NRAS</i>	4.69%	47.18%	50.37%
	<i>NPR1</i>	8.87%	60.33%	59.9%
	<i>CFAP221</i>	4.2%	47.54%	48.35%
	<i>TET2</i>	9.75%	51.25%	57.33%
	<i>TET2</i>	7.11%	46.63%	49.16%
	<i>ZNF318</i>	6.08%	41.03%	50.83%
	<i>RIMS1</i>	2.8%	37.96%	22.02%
	<i>CFTR</i>	4.76%	41.46%	46.67%
	<i>ANK1</i>	8%	57.42%	51.85%
	<i>RSPO2</i>	4.14%	52.14%	43.97%
	<i>ST14</i>	8.62%	47.55%	46.74%
	<i>FOXO1</i>	6.74%	64.1%	37.84%
	<i>FSCB</i>	0%	38.89%	43.33%
	<i>TRIP11</i>	1.4%	20.31%	13.21%
	<i>ALDH1A2</i>	7.07%	52.1%	54.33%
	<i>CDH13</i>	2.41%	39.44%	25.09%
	<i>SRSF2</i>	6.59%	45.74%	49.56%
<i>DOHH</i>	1.08%	34.15%	27.12%	
<i>CENPB</i>	4.97%	49.66%	40.48%	
<i>EMILIN3</i>	7%	43.33%	58.7%	
<b>WES9</b>	<i>FSIP2</i>	3.77%	46.6%	52.38%
	<i>CCDC80</i>	1.7%	16.33%	23.53%



	<i>ILDR1</i>	5.97%	33.33%	50%
	<i>TET2</i>	5.45%	39.02%	48.54%
	<i>TPPP</i>	6.49%	54.22%	69.41%
	<i>PCDHGA1</i>	7.77%	48.24%	42.86%
	<i>DNAH8</i>	7.25%	45.45%	46.46%
	<i>TNFAIP3</i>	8.62%	48.48%	38.64%
	<i>CHRNA6</i>	1.23%	16.2%	10.62%
	<i>C10orf71</i>	7.61%	51.9%	38.46%
	<i>OR9G1;OR9G9</i>	4.27%	18.89%	29.89%
	<i>AHNAK</i>	7.41%	46.49%	41.77%
	<i>CABP2</i>	8.23%	45.59%	42.05%
	<i>ETV6</i>	5.75%	49.64%	44.72%
	<i>PDZRN4</i>	4.55%	47.37%	45.21%
	<i>PIWIL1</i>	5.83%	53.57%	46.67%
	<i>LMO7</i>	2.22%	50.59%	49%
	<i>SETD1A</i>	7.27%	43.97%	40.38%
	<i>PRDM7</i>	9.54%	41.36%	52.34%
	<i>LOC100506388</i>	4.26%	36.59%	42.86%
	<i>HNF1B</i>	4.98%	44.77%	47.65%
	<i>SRSF2</i>	5.13%	43.24%	49.02%
	<i>TSHZ1</i>	0.42%	15.74%	13.09%
	<i>ASXL1</i>	8.15%	46.58%	47.18%
	<i>C1QTNF6</i>	5.83%	54.4%	54.48%
	<i>TUBGCP6</i>	4.51%	50.28%	32.23%
	<i>KRAS</i>	0.51%	7%	11.11%
	<i>RIT1</i>	2.56%	28.87%	14%
<b>WES16</b>	<i>PRAMEF12</i>	3.45%	55%	50%
	<i>SLC25A34</i>	1.1%	46.88%	52.94%
	<i>MPL</i>	1.92%	45.1%	44.04%
	<i>ERICH3</i>	8.75%	51.35%	52.73%
	<i>VAV3</i>	5.32%	45.78%	46.21%
	<i>NRAS</i>	3.64%	40.74%	50%
	<i>CACNA1S</i>	3.7%	44.72%	46.12%
	<i>TET2</i>	7.37%	40.28%	46.51%
	<i>FAT4</i>	2.17%	39.37%	47.49%
	<i>MND1</i>	8.7%	50%	51.43%
	<i>CACNA1B</i>	7.32%	51.85%	55.77%
	<i>IRAK4</i>	9.09%	42.31%	44.68%
	<i>SRCAP</i>	4.68%	48.53%	46.83%
<i>ASXL1</i>	3.57%	36.84%	42.99%	
<b>WES11</b>	<i>PRAMEF12</i>	5.56%	48.15%	41.94%
	<i>INO80B</i>	4.69%	38.64%	56%
	<i>UNC80</i>	8.33%	42.91%	41.46%
	<i>NEK4</i>	9.49%	50%	51.46%
	<i>MARCH11</i>	8.6%	43.09%	32.53%
	<i>NLRP10</i>	8.97%	55.68%	56.14%
	<i>NLRX1</i>	7.6%	54.22%	50%
	<i>UNC79</i>	6.06%	38.17%	44.51%
	<i>MGA</i>	5.63%	43.14%	34.15%
	<i>CDH19</i>	6.94%	50.62%	50%
<i>SRSF2</i>	12%	52%	66%	

	<i>ASXL1</i>	9.67%	29.16%	28.20%
<b>WES14</b>	<i>NRAS</i>	5.56%	42.19%	53.85%
	<i>ACMSD</i>	6.45%	46.51%	42.05%
	<i>SP140</i>	3.45%	44.66%	40.62%
	<i>UGT1A8</i>	9.3%	62.26%	43.14%
	<i>MUC4</i>	0.39%	16.36%	17.51%
	<i>PRSS3</i>	7.21%	23.86%	25.47%
	<i>UBN1</i>	8.57%	53.57%	41.18%
	<i>KCNC3</i>	4.49%	44.24%	42.95%
	<i>ASXL1</i>	5.45%	45%	34.83%
	<i>TET2</i>	15%	59%	46%
	<i>TET2</i>	19%	46.15%	49.09%
	<i>SRSF2</i>	14%	52%	53%
<b>WES13</b>	<i>USH2A</i>	0.91%	45.68%	28.93%
	<i>VAX2</i>	8.39%	47.06%	45.26%
	<i>TET2</i>	9.43%	45.83%	34.85%
	<i>TET2</i>	5%	47.62%	40.74%
	<i>SMAD1</i>	3.75%	46.15%	50.57%
	<i>MUC22</i>	2.29%	14.64%	11.19%
	<i>DPP3</i>	0%	36.36%	42.86%
	<i>CBL</i>	4.95%	82%	79.07%
	<i>SCNN1G</i>	4.35%	52%	51.18%
	<i>KRT16</i>	4.76%	36.21%	31.08%
	<i>TMC8</i>	2.78%	42.22%	56.52%
	<i>RRBP1</i>	3.57%	22.58%	21.33%
<b>WES15</b>	<i>RPTN</i>	0.58%	43.67%	50.99%
	<i>CTNNA2</i>	4.67%	43.59%	48.06%
	<i>ERFE</i>	3.23%	68%	50.98%
	<i>MUC4</i>	0.26%	12.86%	12.25%
	<i>EYS</i>	1.43%	41.77%	46.43%
	<i>RADIL</i>	6.98%	36.21%	47.54%
	<i>EZH2</i>	6.67%	43.3%	39.29%
	<i>SLC46A2</i>	5.19%	55.05%	50.39%
	<i>ARHGAP11A</i>	2.56%	45.83%	44.44%
	<i>ALOX15</i>	5.5%	51.45%	55.96%
	<i>DNAH9</i>	6.78%	40%	56.25%
	<i>SRSF2</i>	8.24%	41.44%	39.47%
	<i>ASXL1</i>	5.41%	45.71%	39.09%
	<i>USH2A</i>	0%	38%	62.5%
<i>TTC39B</i>	9.3%	43.33%	22%	
<b>WES12</b>	<i>CSF3R</i>	5%	88.46%	100%
	<i>CSF3R</i>	1.61%	30.22%	37.41%
	<i>NPAS2</i>	1.69%	41.27%	36.11%
	<i>LCT</i>	3.03%	56%	45.95%
	<i>GATB</i>	0%	37.97%	39.58%
	<i>ASB5</i>	3.57%	41.25%	47.06%
	<i>ZDHHC11</i>	0%	17.21%	25%
	<i>RXRB</i>	3.17%	44.44%	50.99%
	<i>CDK14</i>	1.1%	32.41%	37.66%
	<i>CUX1</i>	0%	48.75%	56.52%
	<i>DEFB105A;DEFB105B</i>	2.04%	29.82%	34.29%

<i>DEFB105A;DEFB105B</i>	0.67%	28.14%	32.76%
<i>FGF20</i>	0.76%	33.33%	39.29%
<i>MMP12</i>	0%	83.97%	91.84%
<i>DAZAP2</i>	6.14%	38.01%	30.34%
<i>LRP1</i>	0.85%	24.09%	32.23%
<i>C15orf39</i>	2%	34.62%	54.17%
<i>ACSF3</i>	0.8%	38.8%	47.56%
<i>KRT28</i>	3.45%	49.17%	50.62%
<i>KRT34</i>	2.7%	38.58%	41.05%
<i>SRSF2</i>	5.71%	38.64%	34.48%
<i>UBA2</i>	0.83%	10.12%	12.5%
<i>USP29</i>	2.33%	39.62%	40%
<i>ASXL1</i>	2.17%	32.65%	54.29%
<i>NBPF3</i>	3.6%	19.4%	12%
<i>ALG14</i>	0%	10.79%	13%
<i>UGDH</i>	4.74%	13%	16.03%
<i>MAP1B</i>	1.52%	5%	11.97%
<i>ZSWIM8</i>	7.34%	15%	23.62%

**Supplemental table 7.** Estimate fixation time (years) in function of relative fitness, derived from a Moran birth-death process. Fixation times have been derived from calculated CMML relative fitness ( $r$ , from 1.08 to 5,  $N=10$ ), in a constant size population of 100,000 stem cells, with different division rates per year ( $d$ , from 0.5 to 3,  $N=6$ ) without (w/o) CXCL8 and with CXCL8. The decrease in fixation time between the condition with CXCL8 and without CXCL8 is calculated (%).

CMML patients	d	Relative fitness ( $r$ )		Fixation time (years)		Decrease in fixation time with CXCL8 compared to w/o CXCL8 (%)
		w/o CXCL8	with CXCL8	w/o CXCL8	with CXCL8	
CMML 2574	0.5	1.16	1.49	310.8	117.0	62.4
CMML 2812	0.5	1.67	2.18	91.8	62.1	32.4
CMML 4137	0.5	1.45	1.75	125.4	84.4	32.7
CMML 3073	0.5	1.3	1.6	176.5	99.8	43.5
CMML 2239	0.5	1.53	2.09	109.9	65.3	40.6
CMML 2300	0.5	1.52	2.02	111.6	68.2	38.9
CMML 1565	0.5	1.24	1.58	214.9	102.4	52.3
CMML 1745	0.5	1.07	1.44	680.9	127.7	81.2
CMML 2187	0.5	1.21	1.83	242.3	78.5	67.6
CMML 2415	0.5	1.08	1.66	598.7	92.8	84.5
CMML 2574	1	1.16	1.49	155.4	58.5	62.4
CMML 2812	1	1.67	2.18	45.9	31	32.4
CMML 4137	1	1.45	1.75	62.7	42.2	32.7
CMML 3073	1	1.3	1.6	88.3	49.9	43.5
CMML 2239	1	1.53	2.09	55	32.6	40.6
CMML 2300	1	1.52	2.02	55.8	34.1	38.9
CMML 1565	1	1.24	1.58	107.5	51.2	52.3
CMML 1745	1	1.07	1.44	340.5	63.8	81.2
CMML 2187	1	1.21	1.83	121.2	39.3	67.6
CMML 2415	1	1.08	1.66	299.3	46.4	84.5
CMML 2574	1.5	1.16	1.49	103.6	39	62.4
CMML 2812	1.5	1.67	2.18	30.6	20.7	32.4
CMML 4137	1.5	1.45	1.75	41.8	28.1	32.7
CMML 3073	1.5	1.3	1.6	58.8	33.3	43.5
CMML 2239	1.5	1.53	2.09	36.6	21.8	40.6
CMML 2300	1.5	1.52	2.02	37.2	22.7	38.9
CMML 1565	1.5	1.24	1.58	71.6	34.1	52.3
CMML 1745	1.5	1.07	1.44	227	42.6	81.2
CMML 2187	1.5	1.21	1.83	80.8	26.2	67.6
CMML 2415	1.5	1.08	1.66	199.6	30.9	84.5
CMML 2574	2	1.16	1.49	77.7	29.3	62.4
CMML 2812	2	1.67	2.18	22.9	15.5	32.4
CMML 4137	2	1.45	1.75	31.3	21.1	32.7
CMML 3073	2	1.3	1.6	44.1	24.9	43.5
CMML 2239	2	1.53	2.09	27.5	16.3	40.6
CMML 2300	2	1.52	2.02	27.9	17	38.9
CMML 1565	2	1.24	1.58	53.7	25.6	52.3
CMML 1745	2	1.07	1.44	170.2	31.9	81.2
CMML 2187	2	1.21	1.83	60.6	19.6	67.6
CMML 2415	2	1.08	1.66	149.7	23.2	84.5
CMML 2574	2.5	1.16	1.49	62.2	23.4	62.4
CMML 2812	2.5	1.67	2.18	18.4	12.4	32.4
CMML 4137	2.5	1.45	1.75	25.1	16.9	32.7
CMML 3073	2.5	1.3	1.6	35.3	20	43.5
CMML 2239	2.5	1.53	2.09	22	13.1	40.6
CMML 2300	2.5	1.52	2.02	22.3	13.6	38.9
CMML 1565	2.5	1.24	1.58	43	20.5	52.3
CMML 1745	2.5	1.07	1.44	136.2	25.5	81.2
CMML 2187	2.5	1.21	1.83	48.5	15.7	67.6
CMML 2415	2.5	1.08	1.66	119.7	18.6	84.5
CMML 2574	3	1.16	1.49	51.8	19.5	62.4
CMML 2812	3	1.67	2.18	15.3	10.3	32.4
CMML 4137	3	1.45	1.75	20.9	14.1	32.7
CMML 3073	3	1.3	1.6	29.4	16.6	43.5
CMML 2239	3	1.53	2.09	18.3	10.9	40.6
CMML 2300	3	1.52	2.02	18.6	11.4	38.9
CMML 1565	3	1.24	1.58	35.8	17.1	52.3
CMML 1745	3	1.07	1.44	113.5	21.3	81.2
CMML 2187	3	1.21	1.83	40.4	13.1	67.6
CMML 2415	3	1.08	1.66	99.8	15.5	84.5