CD47 expression in acute myeloid leukemia varies according to genotype

CD47 is a "don't eat me" signal to phagocytes, that is overexpressed in solid and blood tumors and represents a key mechanism of immune evasion in cancer.[1] Engagement of signal-regulating protein α (SIRPα) on phagocytic cells by CD47 prevents phagocytosis of tumor cells.[1] In acute myeloid leukemia (AML), CD47 is known to be upregulated on leukemia stem cells (LSC) to avoid phagocytosis[2,3] and increased expression of CD47 commonly predicts worse overall survival.[3] CD47-directed blocking monoclonal antibodies are effective against AML engraftment in preclinical models, by inducing phagocytosis of LSC,[3] and several clinical trials are currently evaluating the efficacy of the Hu5F9-G4 monoclonal antibody magrolimab, alone or in combination with other anti-leukemic compounds in adult AML patients. Early results from two phase Ib trials have shown some clinical efficacy of anti-CD47/magrolimab in AML,[4,5] but solid data on the leukemic patients who are more likely to benefit from this immunotherapeutic approach, according to the underlying genotype, is still lacking.

Here, we provide a detailed immunohistochemical characterization of CD47 protein expression on leukemic cells from formalin- or B5-fixed paraffin-embedded bone marrow sections across AML genomic spectrum, according to 2022 European-LeukemiaNET (ELN) risk stratification, and complement it with bulk transcriptome analysis of leukemic cells from AML patients included in the Beat-AML dataset.[6]

We investigated a cohort of adult AML patients (n=53) from University College of London Cancer Center, London, UK, and the Institute of Hematology, University Hospital of Perugia, Italy. Risk stratification was as follows: 19 of 53 (36%) had low-risk, 19 of 53 (36%) intermediate-risk, and 15 of 53 (28%) adverse-risk AML. Low-risk AML included three (16%) cases with *RUNX1/RUNX1T1*, eight (42%) with *CBFβ/MYH11* and eight (42%) patients with *NPM1*^{mut}*FLT3*^{wt} AML. The intermediate-risk category included seven (37%) patients with *NPM1*^{mut}*FLT3*-internal tandem dublication (ITD), four (21%) with *NPM1*^{wt}*FLT3-ITD* and eight (42%) with *KMT2A/MLLT3*-rearranged AML. The adverse-risk category included five (33%) patients carrying *KMT2A*-rearranged AML (other than *KMT2A/MLLT3* fusion), three (20%) having chromosome 3 aberrations, four (27%) with monosomy 7, and three (20%) with a complex karyotype. The clinicopathologic features of the study cohort are summarized in Table 1. Immunostaining for CD47 of bone marrow (BM) biopsy specimens from AML patients was performed using the recombinant rabbit monoclonal anti-CD47 antibody, EPR21794 clone (Abcam, ab218810); notably, the anti-CD47 antibody (EPR21794 clone) used in this study, as well as the Hu5F9-G4 monoclonal antibody magrolimab,[7] are both raised against the extracellular domain of the human CD47 molecule. The immunostaining procedure was carried out as previously described.[8] In details, the anti-CD47 antibody was tested with similar results in both the BOND-III AutoStainer (Leica Microsystems, Newcastle-upon-Tyne, UK) and the Benchmark ULTRA (VENTANA/ROCHE Diagnostics, Tucson, AZ, USA). The antigen retrieval method was the same for both platforms, as was the EDTA pH-9 based procedure. The HRP-labeled polymers were used as per suppliers' specification and DAB was applied to detect the antigen-antibody reaction. The BOND-III AutoStainer platform was then used to perform the whole series of staining. The CD47 immunohistochemical expression and antigen intensity was scored from 0 to 3 (0: absent membranous staining; 1: weak; 2: moderate: 3: strong) and independently assessed by three investigators (AM, BF, and TM). Fixation methods did not influence CD47 antigen detection or intensity; as such, results from our analysis appeared fixation-independent across all genomic subtypes of AML.

In the low-risk category, 16 of 19 cases had strong CD47 expression, while, among the remaining three cases, two of three (67%) with *RUNX1/RUNXT1* and one of eight (12.5%) with *NPM1*^{mut} AML showed weak expression (intensity score: 1). In particular, all *CBFβ/MYH11* AML samples (n=8) showed a diffuse and strong (intensity score: 3) expression of CD47 on leukemic blasts (Figure 1A, B; Table 1). This was in keeping with the levels of *CD47* mRNA in leukemic cells from patients with *CBFβ/MYH11* AML, included in the Beat-AML project dataset.[6] Indeed, *CBFβ/MYH11* AML consistently showed an elevated expression of the *CD47* gene transcript compared to other genomic subtypes, such as *RUNX1/RUNX1T1* or *KMT2A/MLLT3* (Figure 2). Notably, *CBFβ/MYH11* AML cases bearing *KIT*-D816V mutations included in the Beat-AML dataset, all clustered within the CD47-high subgroup (n=4/9, Fisher-exact test; *P*=0.08), that has been stratified according to the median normalized expression of the *CD47* gene transcript. However, in our study cohort, only one patient (1/8) with *CBFβ/MYH11* AML was *KIT*^{D816V}-mutated, thereby precluding validation by immunohistochemistry of the transcriptomic analysis performed with the Beat-AML dataset.[6] Among AML cases carrying an *NPM1* mutation (n=15), 13 of 15 were positive for CD47, but two of 13 (15%) had weak expression (intensity score: 1) (Table 1). Our results were in keeping with a previous tissue microarray study,[9] pointing to a significant association between an increased CD47 expression and the presence of *NPM1* mutation, but not of *FLT3*-ITD mutation. Accordingly,

Table 1. Demographic, diagnostic features and immunohistochemical analysis of CD47 antigen expression in the acute myeloid leukemia patients' cohort.

	ID	Age in yrs	Sex	Blast percentage	Blast phenotype	CD47 expression	CD47 intensity score
Low-risk category							
RUNX1/RUNX1T1	1	44	M	90-95	$CD34^{+}$, MPO^{+}/dot-like, $CD15^{-/+}$ focal, $CD68^{-}$, $CD117^{+}$	Positive	3
	2	25	M	90	$CD34^{-}$, MPO^{+}, CD68 weak	Weak	1
	3	56	M	95	$CD34^{-/+}$, MPO^{+}, $CD68^{-}$/weak	Weak	1
CBFβ/MYH11	4	45	M	Diffuse	$CD34^{+/-}$, $MPO^{-/+}$, $CD68^{+/-}$	Positive	3
	5	79	F	90	$CD34^{+}$ (10-15%), $MPO^{+/-}$, $CD68^{+/-}$	Positive	3
	6	54	M	Diffuse	$CD34^{-/+}$, MPO^{+}, $CD68^{+}$	Positive	3
	7	41	M	Diffuse	$CD34^{+}$ (15%), $MPO^{+/-}$, $CD68^{+/-}$	Positive	3
	8	62	M	Diffuse	$CD34^{-/+}$, $MPO^{-/+}$, $CD68^{-/+}$	Positive	3
	9	71	M	30-40	$CD34^{+}$ (10-15%),$MPO^{+/-}$, $CD68^{-/+}$	Positive	3
	10	50	M	Diffuse	$CD34^{-/+}$, $MPO^{+/-}$, $CD68^{-/+}$	Positive	3
	11	28	F	5-10	$CD34^{+}$ (5-10%), $CD117^{+}$ (15%), $CD38^{-}$/weak	Positive	3
NPM1^{mut} *FLT3*^{wt}	12	74	F	80	$CD34^{-}$, $MPO^{+/-}$, $CD68^{-/+}$	Negative/weak	1
	13	66	M	90	$CD34^{-}$, $MPO^{-/+}$, $CD68^{+/-}$	Positive	3
	14	56	F	95	$CD34^{-}$, MPO^{+}, $CD68^{-}$	Positive	3
	15	43	F	Diffuse	$CD34^{-}$, MPO^{+}, $CD68^{-/+}$	Positive	3
	16	66	M	60-70	$CD34^{-}$, $MPO^{-/+}$, $CD68^{+/-}$	Positive	3
	17	53	M	Diffuse	$CD34^{-}$, $MPO^{+/-}$, $CD68^{-/+}$	Positive	3
	18	47	M	>90	$CD34^{-}$, $CD33^{+}$, $CD117^{+}$ (10-15%), MPO^{+} (10-15%)	Positive	3
	19	65	M	Diffuse	$CD34^{-}$, CD117 very weak, MPO focal	Positive	3
Intermediate-risk category							
NPM1^{mut} *FLT3*-ITD	20	62	F	Diffuse	$CD34^{-}$, $MPO^{-/+}$, $CD68^{-/+}$	Weak	1
	21	27	F	Diffuse	$CD34^{-}$, MPO^{+}, $CD68^{-}$	Positive	3
	22	48	M	Diffuse	$CD34^{-}$, $MPO^{-/+}$, $CD68^{-/+}$	Positive	3
	23	52	M	90	$CD34^{-}$, MPO^{-}, $CD68^{-/+}$	Positive	3
	24	79	F	Diffuse	$CD34^{-}$, MPO^{+}, $CD68^{-}$	Positive	3
	25	70	F	90-95	$CD34^{-}$, MPO^{+}/focal, $CD68^{+}$	Negative	0
	26	54	M	95	$CD33^{+}$, $CD34^{-}$, $CD117^{-}$	Negative	0
NPM1^{wt} *FLT3*-ITD	27	73	M	40	$CD34^{+}$ (4-5%), $MPO^{+/-}$ weak, $CD68^{+/-}$	Weak	1
	28	73	F	Diffuse	$CD34^{+}$ (5%), $MPO^{+/-}$, $CD68^{+/-}$	Focal positive (20-30%)	1
	29	84	M	90-95	$CD34^{-}$, MPO^{+}/weak, $CD68^{+}$	Negative	0
	30	76	F	Diffuse	$CD34^{+}$, $MPO^{+/-}$ weak, $CD68^{-}$	Negative	0
KMT2A/MLLT3	31	57	M	90-95	$CD34^{-}$, $MPO^{+/-}$, $PGM1^{+/-}$	Negative	0
	32	17	M	100	$CD34^{-}$, $CD117^{-}$, $CD33^{+}$, MPO^{-}, TdT^{-}	Negative	0
	33	16	F	100	$CD34^{-}$, $CD117^{-}$, MPO^{+}	Negative	0
	34	32	F	80	$CD34^{-}$, $CD38^{-}$, $CD117^{+}$, $CD11c^{+}$, MPO^{+}	Negative	0
	35	65	F	>90	$CD34^{+}$, $CD117^{+}$/weak, MPO focal weak	Weak	1
	36	69	F	40	$CD34^{-}$, $CD117^{-}$, MPO^{-}, $CD11c^{+}$, $CD68^{+}$	Negative	0
	37	47	M	100	$CD34^{+}$, $CD117^{+}$ (6%)	Weak	1
	38	33	M	95	$CD34^{-}$, MPO weak, $CD68^{+}$, $CD117^{+}$ focal, $CD33^{+}$, CD14 weak	Weak	1
Adverse-risk category							
KMT2A-rearranged*	39	24	M	Diffuse	$CD34^{+}$ (40-50%), $CD117^{+}$ (40-50%)	Negative	0
	40	26	M	25-30	$CD34^{+}$, $CD117^{+}$	Negative	0
	41	57	F	Diffuse	$CD34^{-}$, $MPO^{-/+}$, $CD68^{-/+}$	Negative/weak	0/1
	42	59	M	Diffuse	$CD34^{-}$, $MPO^{-/+}$, $CD68^{+}$	Negative	0
	43	34	F	90-95	$CD34^{+}$ (20-25%), $MPO^{-/+}$, $CD68^{-/+}$	Weak	1
3q rearrangements	44	74	M	70-80	$CD34^{+}$ (40%), CD117 weak, MPO focal weak, $CD68^{-}$	Positive	3
	45	62	M	80	$CD34^{+}$, $MPO^{+/-}$, CD68 focal weak	Weak	1
	46	57	M	90	$CD34^{+/-}$, MPO focal weak, $CD68^{+}$ focal	Positive	3
Monosomy 7	47	64	F	40	$CD34^{+/-}$, MPO^{+}, $CD68^{-}$	Weak	1
	48	64	F	95	$CD34^{+}$, $MPO^{+/-}$, $CD68^{+/-}$	Negative	0
	49	57	F	Diffuse	$CD34^{-}$, MPO^{+}, $CD68^{+}$ focal	Positive	3
	50	57	F	90	$CD34^{+}$, MPO^{+}, $CD68^{-}$	Positive	3
Complex karyotype	51	62	M	Diffuse	$CD34^{+}$, MPO^{+}, $CD68^{-}$	Focal weak	1
	52	62	M	20-25	$CD34^{+}$	Positive	2
	53	67	F	20	$CD34^{+}$	Positive	2

Continued on following page.

Detailed are the demographic characteristics of the study cohort, including patient's sex and age at acute myeloid leukemia (AML) diagnosis. Blast percentage and phenotype were evaluated on the diagnostic bone marrow biopsy specimen. CD47 expression was then assessed and scored according to differential grades of antigen immunoreactivity (score 0=negative; score 1=weak positive; score 2=moderate positive; score 3=strong positive) from 3 investigators (AM, BF and TM). **KMT2A*-rearranged AML cases had genetic abnormalities other than *KMT2A/MLLT3* fusion. yrs: years; mut: mutated; wt: wild-type; ITD: internal tandem duplication. +/-: in case of >50% positivity of AML cells; -/+: in case of <50% positivity of AML cells.

in our cohort, two of four *NPM1*^{wt}*FLT3*-ITD mutated AML patients had negative CD47 expression on leukemic cells, and the other two cases had weak (ID 27) or focal positive (ID 28) expression of CD47 antigen (Table 1).

Interestingly, all AML patients carrying K*MT2A/MLLT3* (n=8) and *KMT2Ar* (n=5), respectively included in the intermediate- and adverse-risk ELN genomic categories, showed no/low expression of CD47 on leukemic blasts (Table 1), with four of 13 cases (30%) having low expression (intensity score: 1; Figure 1C, D) while the other nine cases displayed complete absence of CD47 antigen expression (intensity score: 0; Figure 1E, F). Notably, the immunohistochemical findings in the *KMT2A/MLLT3* subgroup of AML patients were in keeping with bulk transcriptome analysis performed with the Beat-AML dataset[6] (Figure 2) and were supported by previous studies with *KMT2A/MLLT3* rearranged AML cell lines showing low protein levels of CD47 by western blot.[2]

In the adverse-risk category, which included patients with complex karyotype (n=3), monosomy 7 (n=4), *KMT2A* (n=5) or 3q rearrangements (n=3), 11 of 15 (73%) had positive CD47 expression, including five of 11 cases with weak (intensity score: 1), two of 11 with moderate (intensity score: 2) and four of 11 with strong (intensity score: 3) immunohistochemical expression (Table 1). Unfortunately, the limited number of *TP53*-mutated AML cases (patients ID 52 and 53; Table 1), both of whom demonstrated moderate expression of CD47 (intensity score: 2), precluded any further insights into this very high-risk disease setting, so it

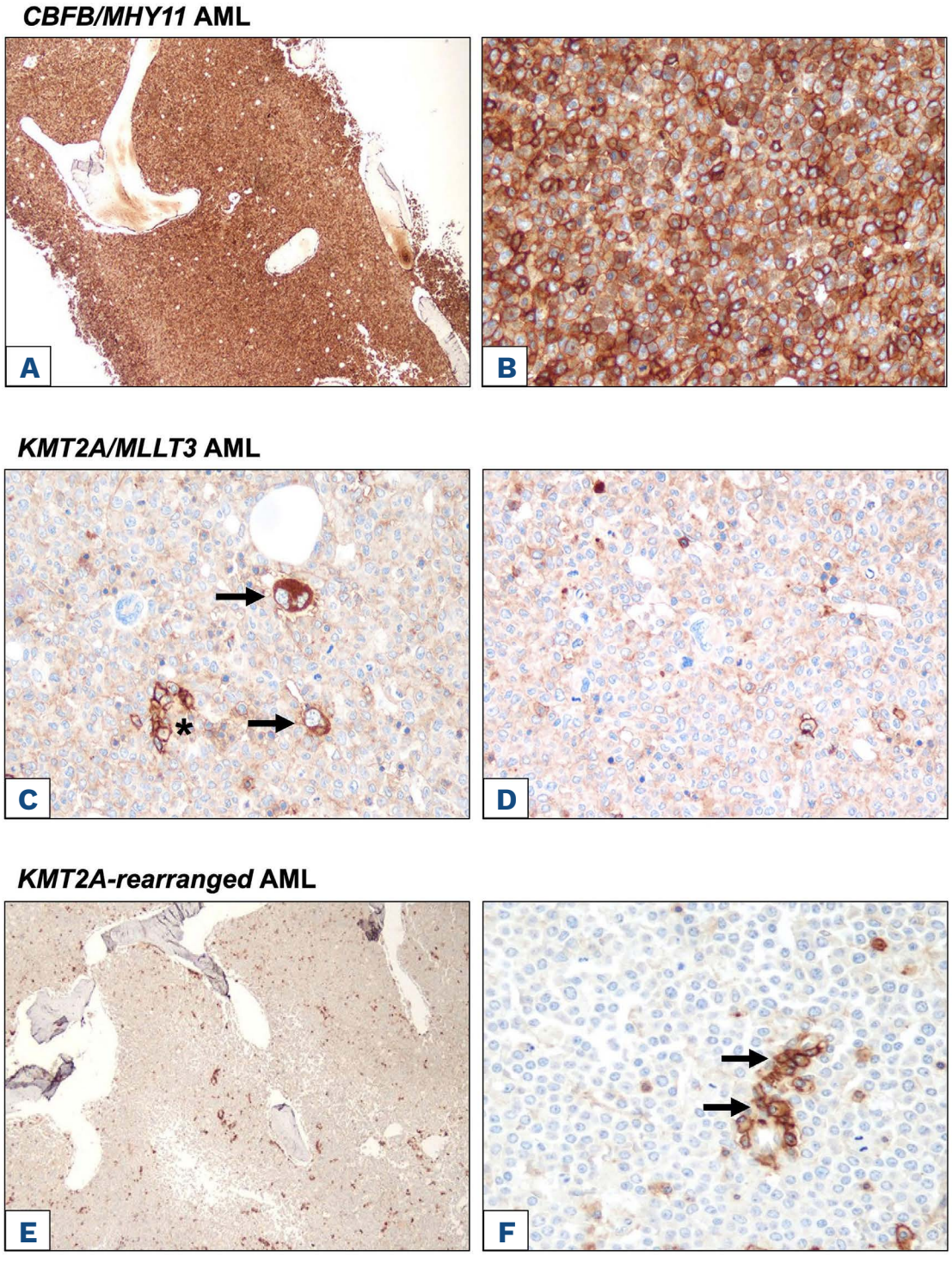

Figure 1. Immunohistochemical expression of CD47 immune antigen across genomic subtypes of acute myeloid leukemia. (A and B) Strong positive (intensity score: 3) and diffuse expression of CD47 by leukemic cells in a patient with *CBFβ/MYH11*-rearranged acute myeloid leukemia (AML, original magnification 4X (A) and 40X (B)). (C and D) CD47-weak positive expression (intensity score: 1) by leukemic cells in a patient with *KMT2A/MLLT3*-rearranged AML. Focal strong staining (black arrows) is seen in background dysplastic megakaryocytes and scattered small cells with round regular nuclei probably of lymphoid origin (asterisk) (original magnification 40X). (E and F) CD47-negative expression (intensity score: 0) by leukemic cells (E and F) in a patient with *KMT2A*-rearranged AML. Scattered background positive small/medium-sized rounded cells, most likely of lymphoid origin, show membranous CD47 expression (F, black arrows) (original magnification 40X). Immunostaining for CD47 was performed using recombinant anti-CD47 antibody, EPR21794 clone, Abcam.

is not clear if such cases could benefit from anti-CD47/magrolimab immunotherapy as suggested by preliminary results from *clinicaltrials gov. Identifier: NCT03248479 trial*.[5] In this study, we have reported that adult AML shows differential patterns of expression of the CD47 immune molecule on leukemic cells. Importantly, *KMT2A/MLLT3* and *KMT2A*-rearranged AML cells were mostly negative for CD47, supporting the use of drugs forcing CD47 antigen expression, such as the hypomethylating agent azacitidine,[10] in combination with anti-CD47 immunotherapy.[1,4,5] Conversely, CD47 was strongly and consistently expressed in *CBFβ/MYH11* AML as well as in the majority of *NPM1*-mutated AML cases (in the absence of *FLT3*-ITD mutation), which suggest these patients may respond better to anti-CD47/magrolimab immunotherapy, urging clinical trials to address this issue. To date, no study has previously evaluated the importance of measuring CD47 antigen density on AML blasts by immunohistochemistry in whole BM section, as well as its relative impact on predicting response to anti-CD47 immunotherapy. However, our data strongly encourage to assess CD47 antigen density in each AML patient undergoing a magrolimab-based treatment.

Emerging results from clinical trials are suggesting that magrolimab holds promise to be effective against high-risk genetic AML category,[4,5] which, in our study cohort, was found to have a lower expression of CD47 molecule compared to other categories. Although we cannot exclude that even a small amount of CD47 antigen could mediate response to magrolimab, it should be noted that in the mentioned clinical trials,[4,5] anti-CD47 immunotherapy was combined to azacitidine, an hypomethylating agent being reported to i) increase CD47 expression,[10] ii) upregulate eat-me signals, as calreticulin[10] and iii) enhance phagocytosis of leukemic cells, thereby acting synergistically with 5F9 (magrolimab).[11,12] Thus, such therapeutic approach may prove effective in treating even AML cases with low levels of CD47 antigen expression on leukemic cells, as those herein more frequently found within the high-risk genetic category. In conclusion, this is the first report quantitatively assessing the immunohistochemical expression of CD47 immune antigen on leukemic cells across distinct genomic subtypes of AML, thus providing a potentially useful guide to immunotherapeutic approaches targeting CD47/SIRPα axis in AML.

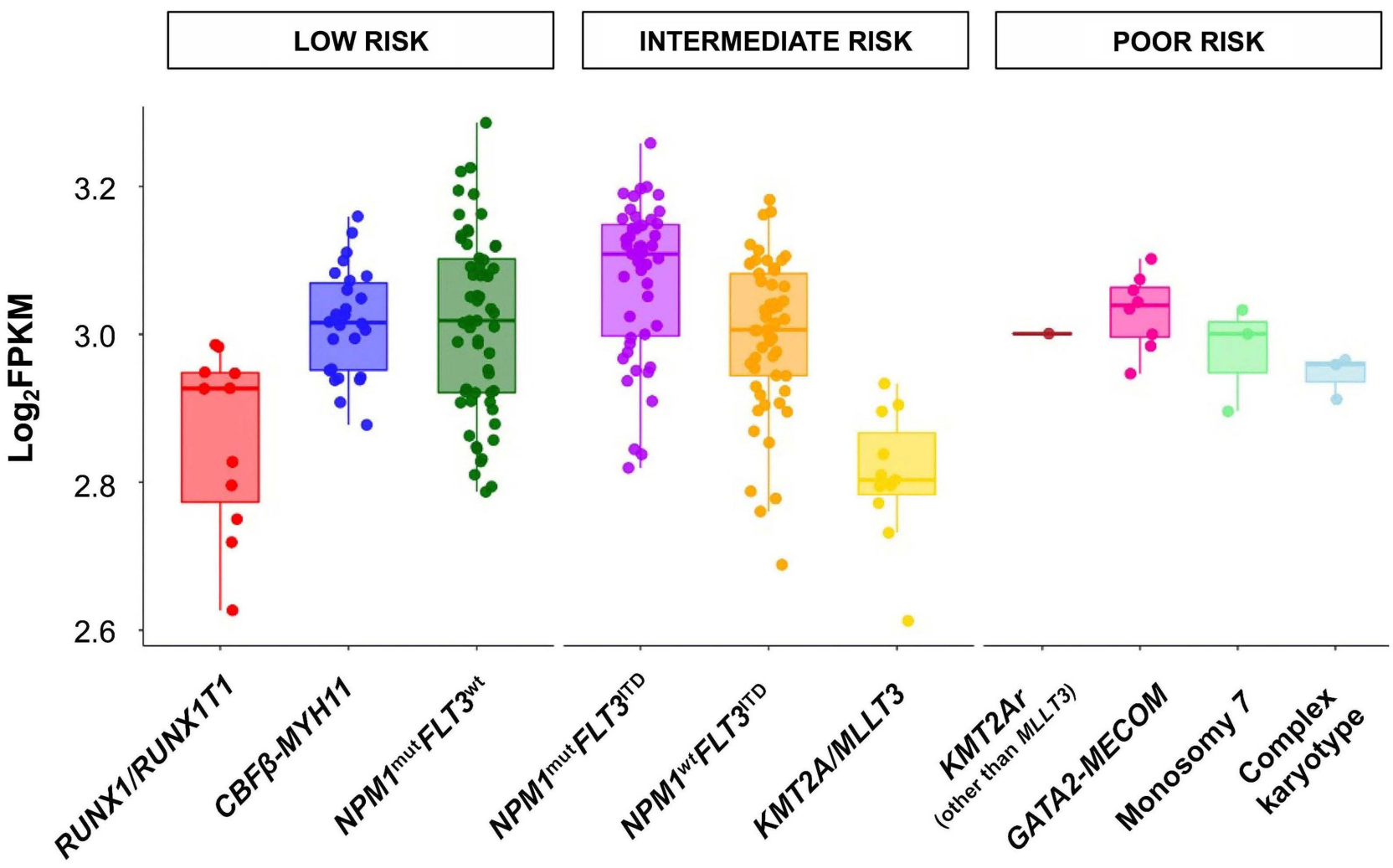

Figure 2. *CD47* mRNA expression across genomic subtypes of acute myeloid leukemia. Transcriptomic data were retrieved from the "Beat-AML" project (http://www.vizome.org/). Bioinformatic and statistics analyses were performed on RNA-sequencing data from bone marrow (BM) samples. Fragments per kilobase of transcript per million mapped reads (FPKM) values for each gene/sample were calculated from RNA-sequencing raw counts, using rpkm function of "edgeR" (R package). According to European LeukemiaNet genetic-risk categories, 10 distinct genomic subgroups of acute myeloid (AML) were identified: the low-risk category includes *RUNX1/RUNX1T1*, *CBFβ/MYH11* and *NPM1*^{mut}*FLT3*^{wt} genotypes; the intermediate-risk category includes *NPM1*^{mut}*FLT3*-internal tandem duplication (ITD), *NPM1*^{wt}*FLT3*-ITD and *KMT2A/MLLT3* genotypes; the high-risk category includes AML cases with the following genotypes, as *KMT2A*-rearrangement (other than *KMT2A/MLLT3*), *GATA2/MECOM*, monosomy 7, and complex karyotype.

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BF licensed a patent on NPM1 mutants (n. 102004901256449) and declares honoraria from Rasna Therapeutics, Inc. for scientific advisor activities. BF is a member of the Neogenomics scientific advisory board. MPM declares honoraria/consultancy at scientific advisory board for AbbVie, Amgen, Celgene, Janssen, Novartis, Pfizer and Jazz Pharmaceuticals. The other authors declare no competing financial interests.

Contributions

AM, BF and TM conceived the study and designed the research. AM, AUA, BF and TM performed most of the research and analyzed immunohistochemical expression of CD47 in the cross-institutional cohort of patients. AM performed analysis of CD47 mRNA expression across genomic subtypes of AML with the Beat-AML dataset. JO'N, RG and AJW contributed wet clinical diagnosis from the UCL cohort of patients. MPM contributed clinical diagnosis from the Perugia cohort of patients. AA, GM, SP, VMP, SA, AR, AC, IP and MRJ performed pathological examination of AML bone marrow diagnostic specimens. AM, BF and TM wrote the paper with critical input from all the authors. AR, CLC and BF edited the paper. AM, BF and TM directed the study.

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Data-sharing statement

Original data are available upon email request to the corresponding author.

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