

## SUPPLEMENTAL MATERIAL

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**Supplemental Table S1.** Study sites and principal investigators

<b>Country</b>	<b>Study site (Principal investigator)</b>
Austria	St. Anna Kinderspital - Hospital (Michael Dworzak)
Belgium	UZ Gent – Hospital (Barbara De Moerloose); Hôpital Universitaire des Enfants Reine Fabiola (Alina Ferster)
Czech Republic	Fakultní nemocnice v Motole (Jan Starý)
Denmark	Rigshospitalet (Karsten Nysom)
France	Hôpital Robert Debré (André Baruchel); Centre Hospitalier Universitaire Lyon (Yves Bertrand); Hopitaux de La Timone (Gérard Michel)
Germany	Universitätsklinikum Düsseldorf (Arndt Borkhardt); Universitätsklinikum Schleswig-Holstein (Gunnar Cario); Klinikum der Universität Regensburg (Selim Corbacioglu); Universitätsklinikum Augsburg (Michael Frühwald); Universitätsklinikum Jena (Bernd Gruhn); Universitätsklinikum Tübingen (Rupert Handgretinger); Universitätsklinikum Frankfurt (Thomas Klingebiel); Medizinische Hochschule Hannover (Christian Kratz); Universitätsklinikum Freiburg (Charlotte Niemeyer); Universitätsklinikum Essen (Dirk Reinhardt); Universitätsklinikum Münster (Claudia Rössig); LMU Klinikum der Universität München (Irene Schmid); Universitätsklinikum Hamburg Eppendorf (Gabriele Escherich, Reinhard Schneppenheim [former]); Charité - Campus Virchow-Klinikum (Karl Seeger); Universitätsklinikum Carl Gustav Carus an der TU Dresden (Meinolf Suttorp)
Ireland	Our Lady's Children's Hospital (Owen Smith)
Italy	Azienda Ospedaliera Di Padova (Laura Sainati, Giuseppe Basso [former]); Ospedale Infantile Regina Margherita (Franca Fagioli); U.O di Onco-Ematologia Ospedale Pediatrico Bambino Gesù (Franco Locatelli); Istituto G Gaslini Ospedale Pediatrico IRCCS (Concetta Micalizzi); Azienda Ospedaliero Universitaria Di Bologna - Policlinico S Orsola Malpighi (Andrea Pession); ASST di Monza - Azienda Ospedaliera San Gerardo (Carmelo Rizzari); Fondazione IRCCS Policlinico San Matteo di Pavia (Marco Zecca)
Netherlands	Erasmus MC-Sophia (Christian Michel Zwaan)

Spain	Hospital Sant Joan de Deu (Susana Rives Sola, Albert Catala Temprano [former]); Hospital Universitario Virgen de La Arrixaca (Ana Maria Galera Miñarro); Hospital Infantil Universitario Niño Jesus (Julián Sevilla)
Sweden	Drottning Silvias Barn Och Ungdomssjukhus (Jonas Abrahamsson); Karolinska Universitetssjukhuset Solna Astrid Lindgrens Childrens hospital (Karin Belander Strålin)
Switzerland	Kinderspital Zürich – Eleonorenstiftung (Markus Schmutz)
United Kingdom	Royal Manchester Children's Hospital (John Grainger)

**Supplemental Table S2.** Variables for evaluation of clinical response to azacitidine

Variables for response	Definition of response			Definition of disease progression or relapse (applicable to all patients)
	Assessment of CR and PR is feasible if the following are present before therapy	Requirement for CR for each variable (cCR)	Requirement for PR for each variable (cPR)	Requirement for PD for each variable (cPD)
1) WBC count	$> 20 \times 10^9/L$	$3.0-15.0 \times 10^9/L$	Decrease by $\geq 50\%$ over pretreatment but still $> 15 \times 10^9/L$	<ul style="list-style-type: none"> <li>• Increase by <math>\geq 50\%</math> and <math>\geq 20 \times 10^9/L</math></li> </ul>
2) Myeloid and erythroid precursors and blasts in PB*	$\geq 5\%$	0-1%	Decrease by $\geq 50\%$ over pretreatment but still $\geq 2\%$	<ul style="list-style-type: none"> <li>• Increase from baseline:                             <ul style="list-style-type: none"> <li>○ <math>&lt; 5\%</math>: <math>\geq 50\%</math> increase and <math>\geq 5\%</math></li> <li>○ <math>\geq 5\%</math>: <math>\geq 50\%</math> increase of total % of myeloid and erythroid precursors and blasts</li> </ul> </li> </ul>
3) Platelet count	$< 100 \times 10^9/L$	$> 100 \times 10^9/L$	<p>For patients starting with <math>\geq 20 \times 10^9/L</math> platelets: absolute increase of <math>\geq 30 \times 10^9/L</math></p> <p>For patients starting with <math>&lt; 20 \times 10^9/L</math></p>	<ul style="list-style-type: none"> <li>• Development of transfusion dependency OR</li> <li>• (If patients have the baseline of the platelet count of <math>\geq 30 \times 10^9/L</math>) decrease by <math>\geq 50\%</math> and <math>&lt; 100 \times 10^9/L</math></li> </ul>

			platelets: increase by $\geq 100\%$ and $> 20 \times 10^9/L$	
4) BM blasts	$\geq 5\%$	$< 5\%$	Decreased by $\geq 50\%$ over pretreatment but still $\geq 5\%$	Increase from baseline; $< 5\%$ : $\geq 50\%$ increase and $\geq 5\%$ $\geq 5\%$ : $\geq 50\%$ increase of BM blasts
5) Spleen size a) Clinical evaluation OR	$\geq 2$ cm under the costal margin	No splenomegaly	50% decrease by cm under the costal margin	Increase by $\geq 100\%$ if baseline $< 4$ cm from under the costal margin $\geq 50\%$ if baseline 5-10cm $> 30\%$ if baseline $> 10$ cm
b) Sonography	Length of spleen $\geq 100\%$ of upper limit of normal range	No splenomegaly	$> 25\%$ decrease by length, but still splenomegaly	Increase by $\geq 25\%$ of length
6) Extramedullary disease <sup>†</sup>	Extramedullary leukemic infiltration	No evidence of extramedullary leukemic infiltration in any organ	-	Worsening or new lesions of extramedullary leukemic infiltration

Modified from Ref. 2.

BM, bone marrow; cCR, clinical complete response; cPD, clinical progressive disease; cPR, clinical partial response; CR, complete response; PB, peripheral blood; PD, progressive disease; PR, partial response; WBC, white blood cell.

\* Myeloid precursors include promyelocytes, myelocytes and metamyelocytes. The myeloid and erythroid precursors and blasts in PB are given as % of the total nucleated cells in PB (WBC including erythroblasts).

† Extramedullary disease includes infiltration of skin, lung, and very rarely cranial nerves or central nervous system.

**Supplemental Table S3. Patient characteristics (N = 18)**

Patient ID	Sex, M/F	Age, years	At C1D1												Clinical response to azacytidine		HSCT, yes/no	Status, alive/dead
			Genetics				Spleen size palpation, cm*	PB						BM blast, %	C3D28	C6D28		
			Mutation		Meth. class	Karyotype		HbF, %	WBC, × G/L	Mono, × G/L	Blast, %	Precursor, †	Platelets, × G/L					
1	M	3.4	PTPN11	c.226G>C; [p.E76Q]	HM	N	9	59.1	27.4	2.5	0	8	22 Tx	2	cPD	-	Yes	Alive
2	M	0.7	NRAS	c.181C>A; [p.Q61K]	HM	N	14	16.5	16.4	3.9	6	12	16 Tx	8	cPR	-	Yes	Alive
3	F	1.0	KRAS	c.38G>A; [p.G13D]	IM	-7	8	2.4	8.9	2.0	1	12	61	7	cPR	cPR	Yes	Alive
4	M	2.2	PTPN11	c.227A>G; [p.E76G]	HM	N	4	38.0	34.8	2.8	0	2	24 Tx	1	cPD	-	Yes	Alive
5	M	4.7	PTPN11	c.226G>C; [p.E76Q]	HM	N	8	56.8	15.6	1.4	16	6	19 Tx	10	cPR	-	Yes	Alive
6	M	6.9	NF1	c.1681_1693dup; TGGAATCCTGATG; [p.Ala565Valfs*4]	HM	-Y	2	10.0	23.0	6.4	2	7	43 Tx	6	cPD	-	Yes	Alive
7	M	2.0	NRAS	c.38G>A; [p.G13D]	IM	N	9	20.3	35.7	3.6	1	6	52 Tx	1	cPR	-	Yes	Alive
8	F	1.1	PTPN11	c.218C>T; [p.T73I]	LM	N	4	0.7 <sup>‡</sup>	12.4	4.8	0	4	85 Tx	5	cPR	cPR	Yes	Alive
9	F	0.4	PTPN11	c.226G>A; [p.E76K]	IM	-7	3	38.8	59.0	22.4	6	13	81 <sup>§</sup>	19	cPR	cPR	Yes	Alive
10	M	1.2	PTPN11	c.181G>C; [p.D61H]	LM	N	3.5	7.6	27.5	3.2	0	1	75	12	cPR	-	Yes	Alive
11	F	0.3	PTPN11	c.181G>T; [p.D61Y]	IM	+21 <sup>  </sup>	2	13.2 <sup>‡</sup>	9.4	0.7	2	38	64 Tx	0	cPR	-	Yes	Alive
12	F	3.0	NRAS	c.183A>T; [p.Q61H]	HM	N	6	26.3	9.9	2.2	2	5	26 Tx	6	cPD	-	Yes	Alive
13	F	3.0	PTPN11	c.226G>A; [p.E76K]	HM	N	4	12.0	11.8	0.8	1	0	25 Tx	6	cPD	-	Yes	Alive
14	M	2.9	PTPN11	c.227A>T; [p.E76V]	HM	N	2	16.5	4.3	0.9	0	0	12 Tx	4	cPR	cPR	Yes	Alive
15	M	1.7	PTPN11	c.215C>T; [p.A72V]	IM	-7	4	1.3 <sup>‡</sup>	35.8	7.2	4	7	15 Tx	9	cPR	cCR	Yes	Alive
16	M	3.4	PTPN11	c.214G>A; [p.A72T]	HM	N	4	26.1	45.9	3.2	0	0	30 <sup>§</sup>	3	cPR	-	Yes	Alive
17	F	1.8	PTPN11	c.227A>C; [p.E76A]	HM	del(9) (q12q21)	6	46.8	10.2	0.5	6	10	51 <sup>§</sup>	15	cPD	-	Yes	Dead
18	M	3.5	PTPN11	c.182A>T; [p.D61V]	HM	N	7	43.6	28.0	4.8	2	12	7 Tx	1	PD	-	No	Dead

C, cycle; cCR, clinical complete remission; cPD, clinical progressive disease; cPR, clinical partial remission; D, day; F, female; Meth, methylation; HbF, fetal hemoglobin; HM, high methylation; IM, intermediate methylation; LM, low methylation; M, male; N, normal; PB, peripheral blood; Tx, platelet transfusion for thrombocytopenia; WBC, white blood cell.

\* Palpable below the costal margin.

† Erythroblasts + promyelocytes + metamyelocytes + myelocytes.

‡ Normal for age.

§ Platelet transfusion in cycle 2.

|| Down syndrome.



**Supplemental Table S4.** Platelet count (G/L) on azacitidine therapy (N = 18)

Patient ID	C1D1	C1D28	C2D28	C3D28	C6D28	Clinical response to azacitidine at C3D28
1	22	41 Tx	17 Tx	23 Tx	N/A	cPD
2	16 Tx	23 Tx	48	57	N/A	cPR
3	61	168	218	352	262	cPR
4	24 Tx	91 Tx	64 Tx	63 Tx	N/A	cPD
5	19 Tx	113 Tx	68 Tx	81 Tx		cPR
6	43 Tx	24 Tx	N/A	N/A	N/A	cPD
7	52 Tx	189 Tx	192	263	N/A	cPR
8	85 Tx	370 Tx	292	274	215	cPR
9	81	310 Tx	74	312	170	cPR
10	75	443	279	326	N/A	cPR
11	64 Tx	101 Tx	18 Tx	251 Tx		cPR
12	26 Tx	14 Tx	33 Tx	21 Tx	N/A	cPD
13	25 Tx	12 Tx	22 Tx	10 Tx		cPD
14	12 Tx	190 Tx	147	164	223	cPR
15	15 Tx	148 Tx	88	256 Tx	158	cPR
16	30	138 Tx	32 Tx	132	N/A	cPR
17	51	13 Tx	21 Tx	33 Tx		cPD
18	7 Tx	N/A	N/A	N/A	N/A	cPD

cPD, clinical progressive disease; cPR, clinical partial remission; C, cycle; D, day; N/A, not applicable (patient off study); Tx, platelet transfusion for thrombocytopenia.

**Supplemental Table S5.** Overview of hematopoietic stem cell transplantations (N = 17)

Patient ID	Sex, M/F	Age to HSCT, years	Genetics		AZA therapy	HSCT									
			Genetic subgroup	Methylation class	Clinical response	Time from diagnosis to HSCT, months	Type of donor	Source of stem cells	CD34 + cells, $\times 10^6/\text{kg}$	Preparative regimen	Engraftment, yes/no	Acute GvHD, Grade II-V	Chronic GvHD, yes/no	Outcome	Status from HSCT, months
1	M	3.7	PTPN11	HM	cPD	5.1	UD (10/10)	PB	9.2	BuCyMel	Yes	II	No	cCR	Alive +38
2	M	1.1	NRAS	HM	cPR	5.2	UD (10/10)	PB	8.5	BuCyMel	Yes	No	No	cCR	Alive +23
3	F	1.5	KRAS	IM	cPR	7.9	UD (9/10)	BM	4.4	FluTreoThio	Yes	II	No	cCR	Alive +12
4	M	2.6	PTPN11	HM	cPD	4.9	MSD	BM	6.2	BuCyMel	Yes	I	No	cCR	Alive +25
5*	M	5.1	PTPN11	HM	cPR	5.5	UD (9/10) FD <sup>†</sup> (5/10)	BM PB	4.52 8.08	BuFluMel TBI 2Gy, FluCy	No Yes	No III	No No	Relapse cCR	- Alive +32 <sup>c</sup>
6	M	7.1	NF1	HM	cPD	3.4	MSD	BM	7.6	BuFluMel	Yes	I	Yes	cCR	Alive +19
7	M	2.4	NRAS	IM	cPR	5.1	UD (10/10)	BM	5.8	BuCyMel	Yes	I	No	cCR	Alive +25
8	F	1.6	PTPN11	LM	cPR	7.2	UD (10/10)	BM	11.4	BuCyMel	Yes	No	No	cCR	Alive +34
9	F	1.1	PTPN11	IM	cPR	11.6	UD (10/10)	BM	6.2	BuCyMel	Yes	No	No	cCR	Alive +34
10	M	1.4	PTPN11	LM	cPR	4.2	UD (10/10)	BM	5.3	BuCyMel	Yes	No	No	cCR	Alive +21
11	F	1.9	PTPN11	IM	cPR	20.2	UD (10/10)	BM	5.5	FluTreoThio	Yes	II	No	cCR	Alive +5
12	F	3.5	NRAS	HM	cPD	6.4	UD (10/10)	BM	5.9	BuCyMel	Yes	No	No	cCR	Alive +32
13	F	3.6	PTPN11	HM	cPD	8.2	UD (10/10)	PB	6.1	BuCyMel	Yes	III	No	Relapse	Alive +14

14	M	3.4	PTPN11	HM	cPR	6.7	UD (10/10)	BM	6.6	BuCyMel	Yes	No	No	Relapse <sup>‡</sup>	Alive +15
15	M	2.4	PTPN11	IM	cPR	9.6	UD (10/10)	BM	9.3	BuCyMel	Yes	No	No	cCR	Alive +13
16	M	3.7	PTPN11	HM	cPR	4.1	UD (10/10)	BM	1.5	BuCyMel	Yes	No	No	cCR	Alive +13
17	F	2.1	PTPN11	HM	cPD	4.7	FD <sup>†</sup> (5/10)	PB	5.3	BuCyMel	No	No	-	NRM	Dead, 2

BM, bone marrow; Bu, busulfan; cCR, clinical complete remission; cPD, clinical progressive disease; cPR, clinical partial remission; Cy, cyclophosphamide; F, female; FD, family donor; Flu, fludarabine; HM, high methylation; HSCT, hematopoietic stem cell transplantation; IM, intermediate methylation; LM, low methylation; M, male; Mel, melphalan; MSD, matched sibling donor; NRM, non-relapse mortality; PB, peripheral blood; TBI, total body irradiation; Thio, thiosulfan; Treo, treosulfan; UD, unmatched donor.

\* After primary failure of first engraftment (details and outcome in top row), patient underwent second transplantation (details and outcome in bottom row).

† Haploidentical parent.

‡ As of April 21, 2020.

**Supplemental Table S6.** Azacitidine plasma pharmacokinetic parameters at cycle 1 day 7

Parameter	$C_{max,*}$ ng/mL	$T_{max,*}$ h	$AUC_{0-t,*}$ h*ng/mL	$AUC_{24,*}$ h*ng/mL	$AUC_{0-\infty,†}$ h*ng/mL	$t_{1/2,†}$ h	$CL,†$ L/h	$V_z,†$ L
Geometric mean	1,066.3	0.1	386.9	394.4	240.2	0.3	148.3	61.1
Geometric CV%	215.3	53.4	149.4	145.9	76.5	58.4	104.2	125.8

$AUC_{24}$ , area under the concentration-time curve from time zero to 24 hours;  $AUC_{0-\infty}$ , area under the concentration-time curve from time zero to infinity;  $AUC_{0-t}$ , area under the concentration-time curve from time zero to the last measurable concentration; CL, total body clearance;  $C_{max}$ , maximum plasma drug concentration; CV, coefficient of variation;  $t_{1/2}$ , elimination half-life;  $T_{max}$ , time to reach maximum plasma drug concentration;  $V_z$ , volume of distribution based on terminal phase.

\* Analysis included 18 patients.

† Analysis included 12 patients.

**Supplemental Table S7.** Variant allele frequencies in bone marrow granulocytes under therapy with azacitidine

Patient ID	Variant	C1D1	C3D28	Pre-HSCT	Time from last VAF to HSCT, days
1	PTPN11 c.226G>C; [p.E76Q]	46.85	28.54	N/A	24
2	NRAS c.181C>A; [p.Q61K]	41.50	33.52	N/A	49
3	KRAS c.38G>A; [p.G13D]	39.52	18.87	23.04	15
4	PTPN11 c.227A>G; [p.E76G]	46.19	47.28	48.96	27
5	PTPN11 c.226G>C; [p.E76Q]]	43.89	44.30	N/A	49
7	NRAS c.38G>A; [p.G13D]	46.78	44.84	45.51	14
8	PTPN11 c.218C>T; [p.T73I]	45.18	46.50	46.02	14
9	PTPN11 c.226G>A; [p.E76K]	45.67	32.80	46.07	9
10	PTPN11 c.181G>C; [p.D61H]	45.72	40.41	N/A	16
11	PTPN11 c.181G>T; [p.D61Y]	47.33	47.29	N/A	495
12	NRAS c.183A>T; [p.Q61H]	48.03	55.75	40.34	12

13	PTPN11 c.226G>A; [p.E76K]	44.23	40.08	N/A	129
14	PTPN11 c.227A>T; [p.E76V]	45.51	38.91	27.26	17
15	PTPN11 c.215C>T; [p.A72V]	45.44	N/A	39.81	14
16	PTPN11 c.214G>A; [p.A72T]	46.05	43.98	45.20	10

C, cycle; D, day; HSCT, hematopoietic stem cell transplantation; N/A, not available; VAF, variant allele frequencies.

**Supplemental Table S8.** Incidence of treatment-emergent adverse events

<b>Parameter, n (%)</b>	<b>N = 18</b>
<b>Patients who experienced <math>\geq 1</math> TEAE (any grade; <math>\geq 15\%</math> incidence)</b>	18 (100)
Anemia	7 (39)
Thrombocytopenia*	5 (28)
Vomiting	5 (28)
Constipation	4 (22)
Cough	4 (22)
Diarrhea	4 (22)
Abdominal pain*	3 (17)
Neutropenia	3 (17)
Upper respiratory tract infection†	3 (17)
Pruritus (generalized)	3 (17)
Pruritus	3 (17)
Epistaxis*	3 (17)
Hyperuricemia	3 (17)
<b>Patients who experienced <math>\geq</math> grade 3-4 TEAE</b>	10 (56)
Anemia	6 (33)
Thrombocytopenia*	4 (22)
Diarrhea	1 (6)
Abdominal pain*	2 (11)
Neutropenia	2 (11)
Epistaxis*	1 (6)

<b>Patients who experienced <math>\geq 1</math> treatment-related TEAE</b>	10 (56)
Neutropenia	2 (11)
Anemia	2 (11)
Febrile neutropenia*	1 (6)
Thrombocytopenia*	2 (11)
Vomiting	1 (6)
Constipation	2 (11)
Pyrexia	1 (6)
<b>Patients who experienced <math>\geq 1</math> treatment-related grade 3-4 TEAE</b>	6 (33)
Neutropenia	2 (11)
Anemia	2 (11)
Febrile neutropenia	1 (6)
Thrombocytopenia	1 (6)
Lung infection*	1 (6)

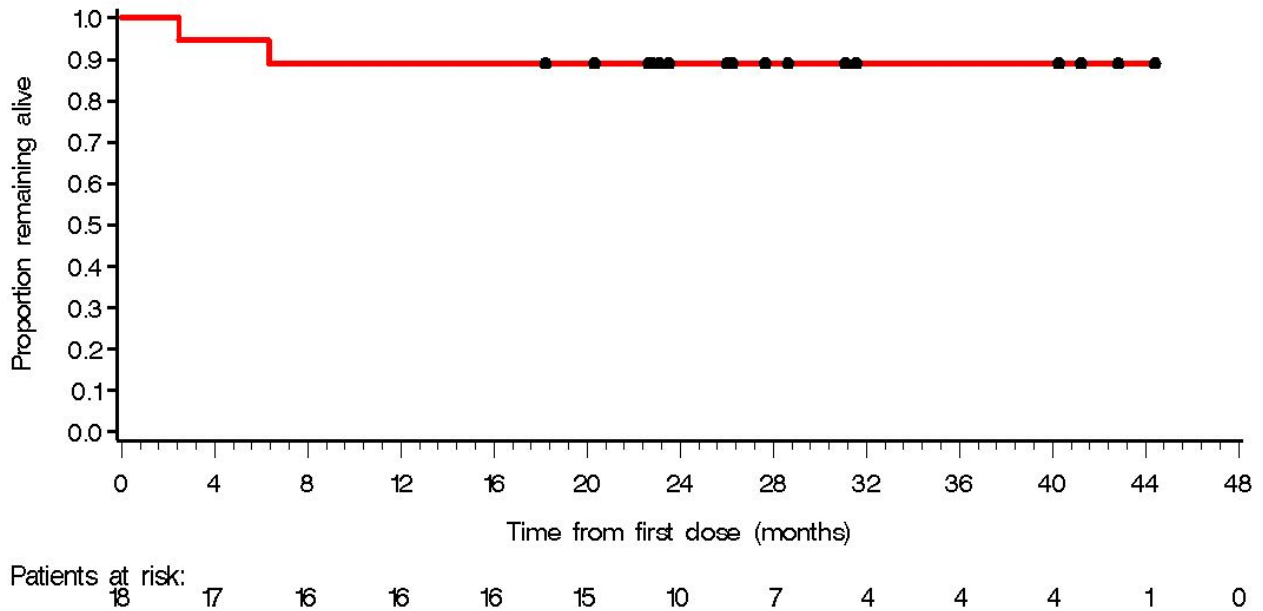
TEAE, treatment-emergent adverse event.

\* Also classified as serious in 1 patient (5.6%).

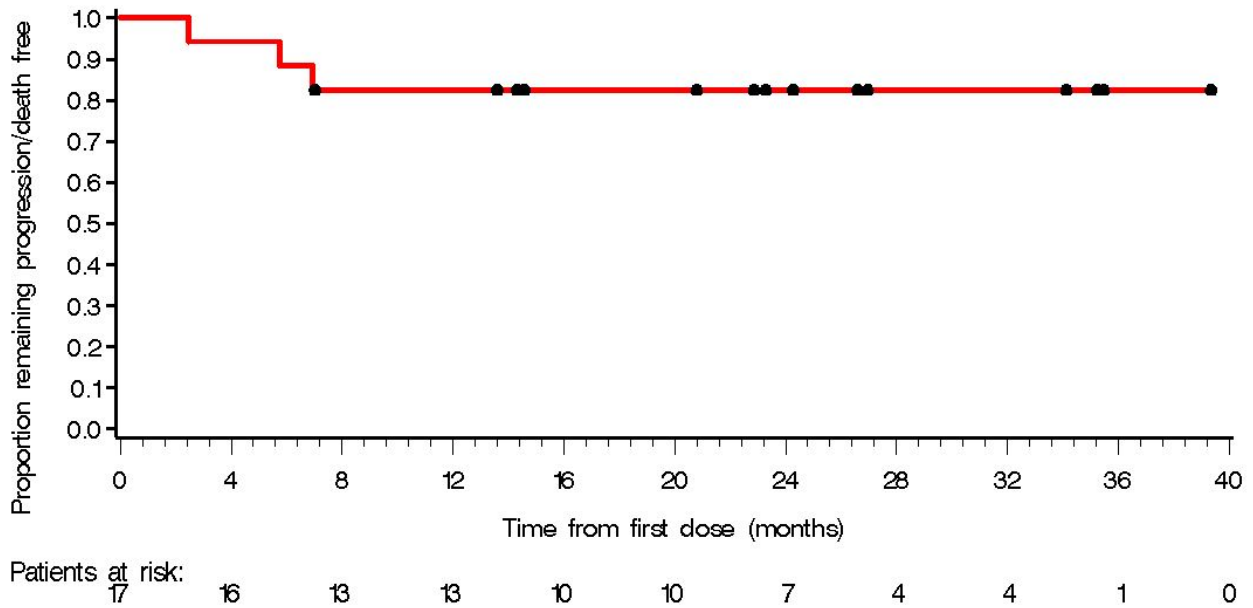
† Also classified as serious in 2 patients (11.1%).



## Overall Survival



## Leukemia Free Survival

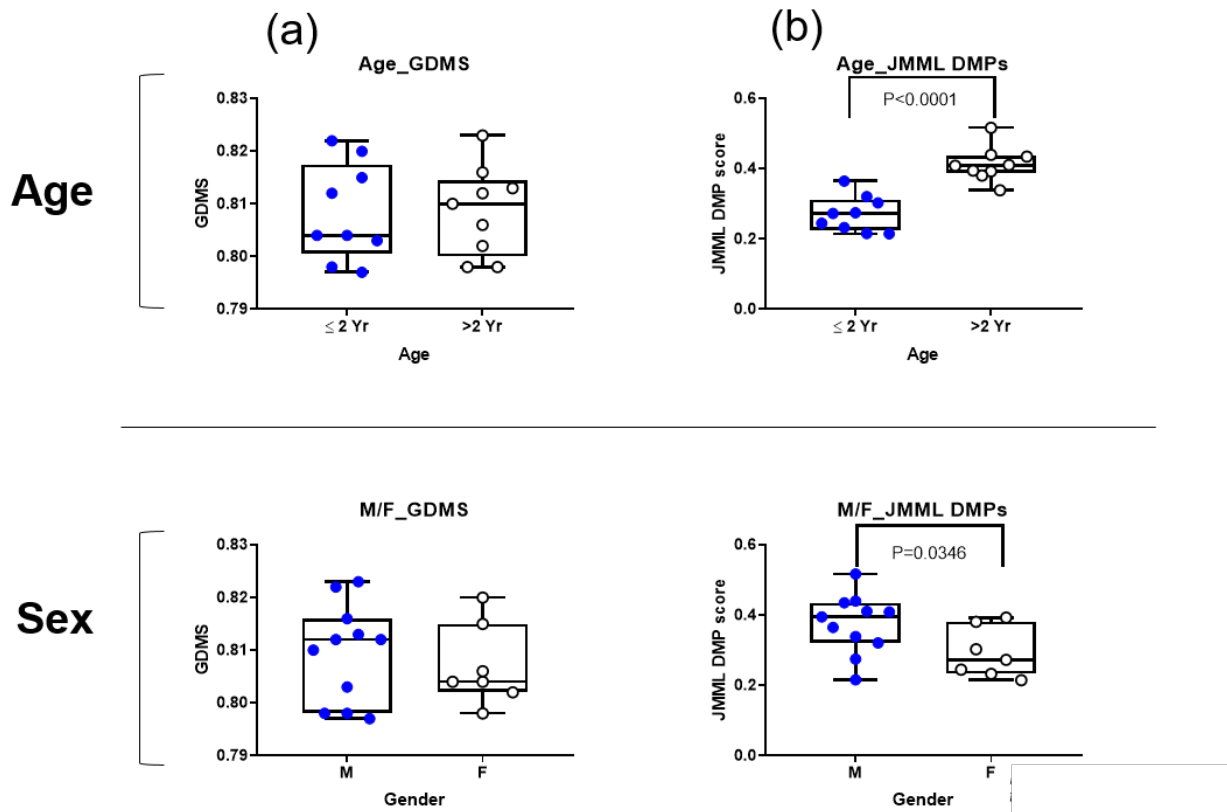


### Supplemental Figure S1. Overall survival and leukemia-free survival in JMML

**cohort.** Overall survival was defined as the time from first study dose day until death from any cause (A). Subjects who are alive at the time of analysis are censored at the

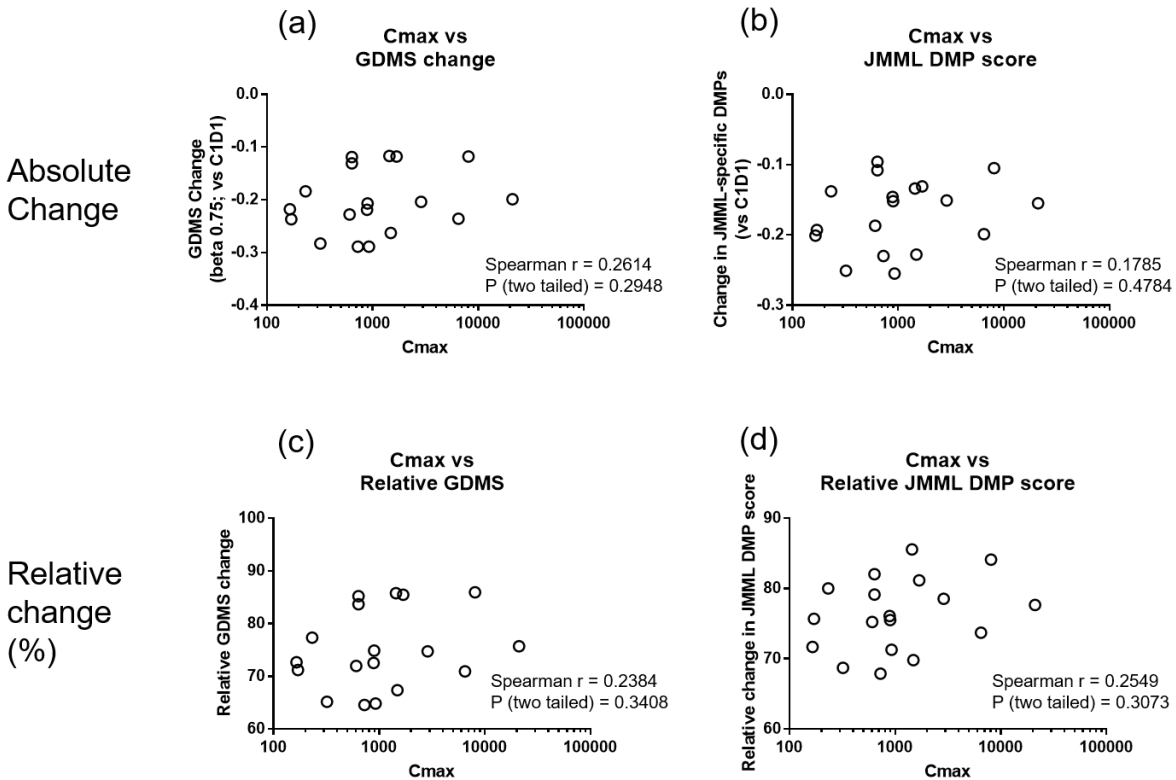
time they were last known to be alive or at clinical cutoff date, whichever was earlier.

Leukemia-free survival was defined as the time from HSCT until leukemia progression or death for subjects receiving HSCT only (B). Subjects who are alive and leukemia-free at the time of the statistical analysis were censored at the time they were last known to be alive. HSCT, hematopoietic stem cell transplantation; JMML, juvenile myelomonocytic leukemia.



**Supplemental Figure S2. DNA methylation levels at baseline in JMML study**

**cohort according to sex and age.** Baseline methylation readouts (absolute values at baseline) stratified by sex (male/M [n = 11] and female/F [n = 7]) and age (subset analysis performed between ≤ 2 years (n = 9) versus > 2 years (n = 9) of (A) GDMS methylation levels (i.e., all CpG probes with beta > 0.75 at pre-dose on cycle 1 day 1) and (B) JDMS derived from differentially methylated probes (JMML DMPs).<sup>1</sup> Statistics performed using a Mann-Whitney two-tailed t-test; significance  $P < .05$ . DMP, differentially methylated position; GDMS, global DNA methylation score; JDMS, JMML-specific DNA methylation score; JMML, juvenile myelomonocytic leukemia.



**Supplemental Figure S3. Relationship of azacitidine plasma concentration and**

**DNA methylation levels in patients with JMML.** Azacitidine maximal observed

plasma concentration ( $C_{max}$ ) at cycle 1 day 7 was computed against the

pharmacodynamic effect (DNA methylation levels) at cycle 1 day 15. Azacitidine

pharmacokinetics was collected at a dose level of 75 mg/m<sup>2</sup> and adjusted for each

patient based on BSA (0.27-7.6 m<sup>2</sup>). Change in GDMS from baseline computed as (A)

absolute difference or (C) relative change of GDMS between baseline and cycle 1 day

15. Change in JDMS derived from differentially methylated probes (JMML DMPs),<sup>1</sup>

shown as (B) absolute difference or (D) relative change between baseline and cycle 1

day 15. BSA, body surface area;  $C_{max}$ , maximum observed plasma concentration; DMP,

differentially methylated position; GDMS, global DNA methylation score; JDMS, JMML-specific DNA methylation score; JMML, juvenile myelomonocytic leukemia.

## References

1. Lipka DB, Witte T, Toth R, et al: RAS-pathway mutation patterns define epigenetic subclasses in juvenile myelomonocytic leukemia. *Nat Commun.* 2017;8(1):2126.
2. Niemeyer CM, Loh ML, Cseh A, et al. Criteria for evaluating response and outcome in clinical trials for children with juvenile myelomonocytic leukemia. *Haematologica.* 2015;100(1):17-22.