

Figure S1. Patient enrollment flow chart. ST, sensitivity test (<70% of analyzed samples); DF, diagnosis failure (without histological evidence of relapsed or refractory acute myeloid leukemia); LE, life expectancy  $\leq 3$  months; SI, systemic antineoplastic therapy within 14 days of study treatment; IC, insufficient cellularity; OR, other reason (death caused by COVID-19 infection).

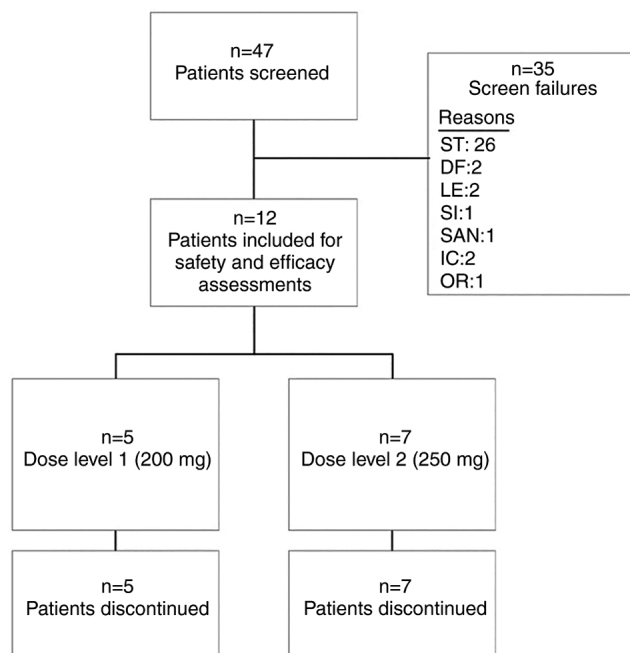
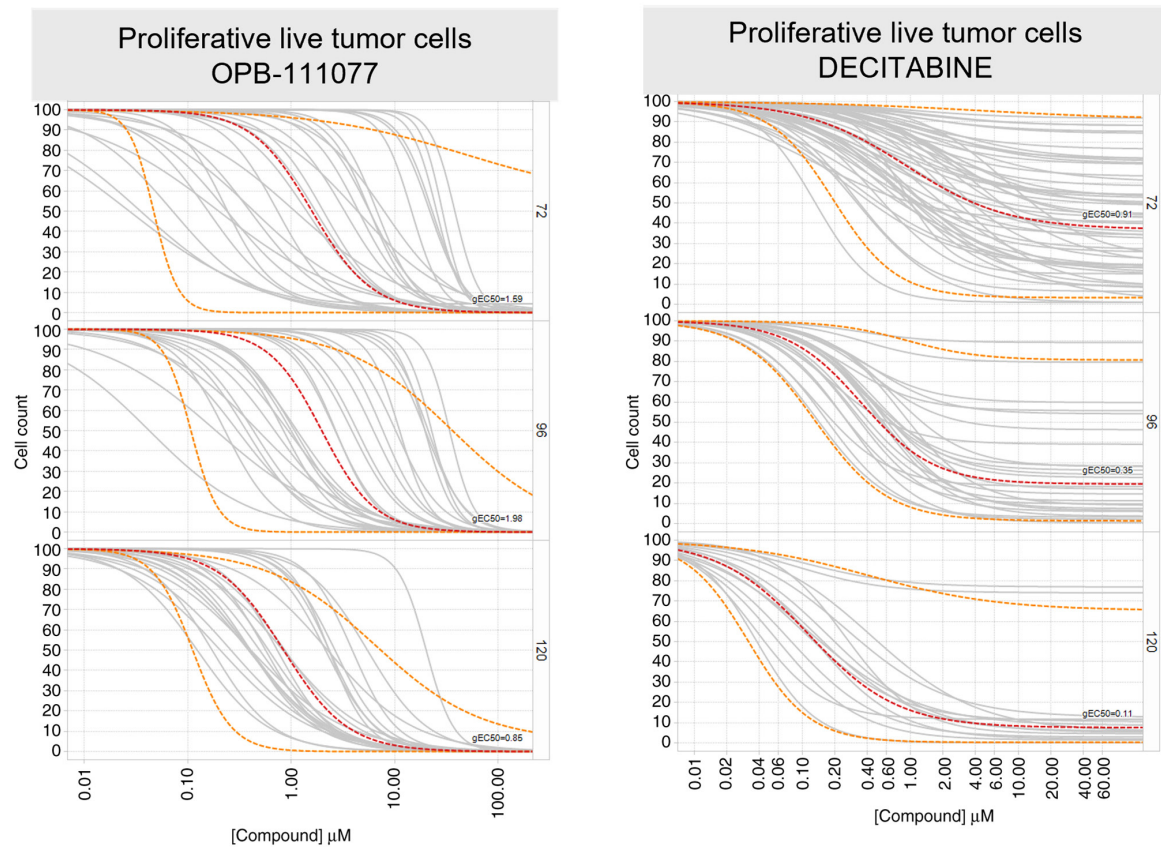


Figure S2. Population curves for OPB-111077 and decitabine. O.F.V\*, objective function; parameters typical and random (variability and residual error) are shown together with the corresponding relative standard error calculated as the ratio between the standard error provided by NONMEM and the estimate. Estimates of inter-patient variability (IPV) are expressed as the coefficient of variation (%).



PD00202						
OPB-111077						
	72		96		120	
	Values	SE(%)	Values	SE(%)	Values	SE(%)
N	27		26		23	
O.F.V*	200.7		127.3		90.9	
E0	1767	30.43	3285	70.68	5296	37.52
Emax	1.00	0.01	1.00	6.28	1.00	0.00
EC50	1.5512	94.88	1.9921	73.28	0.8427	64.91
GAMMA	1.49	23.06	1.68	31.41	1.39	14.78
Additive error	0.4288	11.21	0.4097	21.81	0.4239	9.01
E0.IPV (%)	121.8140	39.77	101.2280	98.54	77.5356	55.69
Emax.IPV (%)	3460.1900	390.09	950.2370	99.60	3510.9300	2730.66
EC50.IPV (%)	444.6880	61.28	310.9270	145.32	153.5090	59.66
GAMMA.IPV (%)	30.0369	53.23	16.9655	211.87	9.2393	52.65
A.Error.IPV (%)	40.3896	25.63	16.4237	148.66	12.2684	57.21

PD00038						
DECITABINE						
	72		96		120	
	Values	SE(%)	Values	SE(%)	Values	SE(%)
N	52		25		14	
O.F.V*	-460.5		-159.7		-154.9	
E0	1482	19.38	2397	25.07	3830	49.15
Emax	0.63	11.99	0.80	0.04	0.93	13.90
EC50	0.9108	20.88	0.3480	58.73	0.1134	19.76
GAMMA	0.93	11.52	1.29	20.55	1.05	15.30
Additive error	0.2216	12.54	0.2814	16.02	0.2124	26.41
E0.IPV (%)	109.8290	25.44	110.7500	53.17	82.3147	47.19
Emax.IPV (%)	301.4090	22.49	300.9720	410.68	379.6860	45.35
EC50.IPV (%)	88.3504	39.18	35.0894	83.64	61.9014	84.75
GAMMA.IPV (%)	8.2206	65.49	0.0000	60.53	5.1747	96421358.41
A.Error.IPV (%)	36.9259	22.57	42.0754	39.35	32.9384	53.27

Figure S3. Overlapped populational curves of OPB-111077 and decitabine.

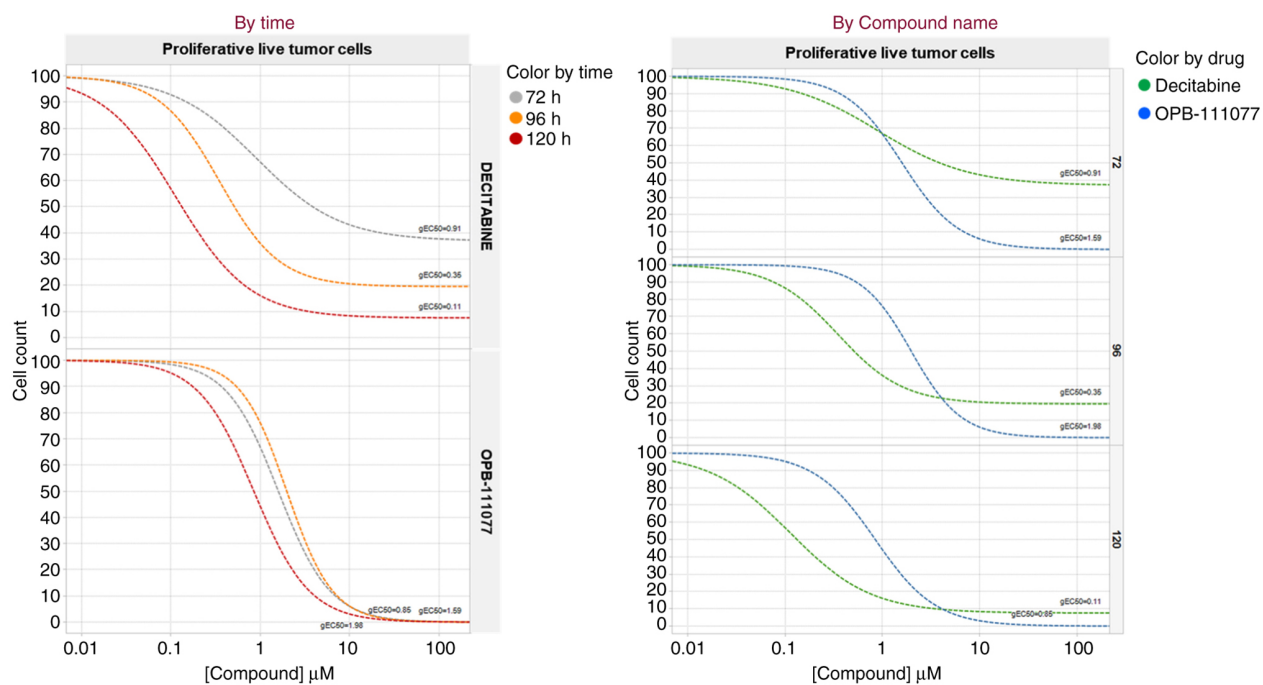


Figure S4. Cumulative progression-free survival. Kaplan-Meier survival curve. Median PFS (95% CI), 57.000 (36.631-77.369).

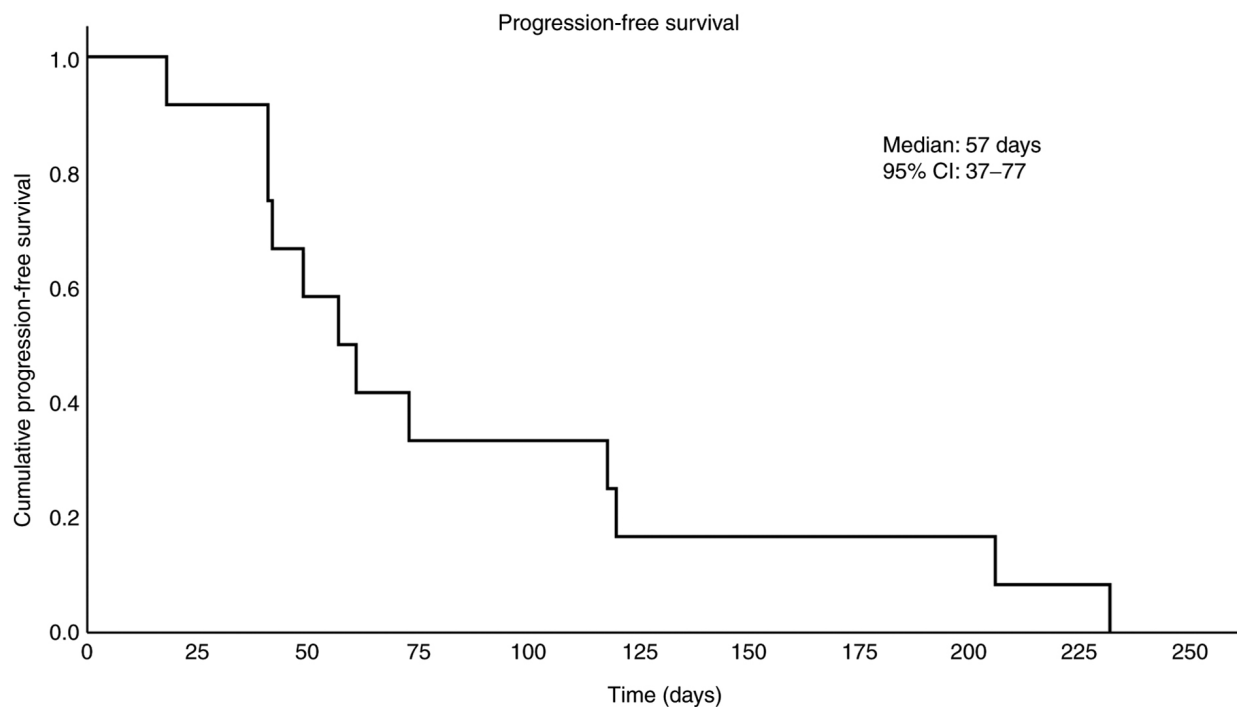


Figure S5. Overall survival. Kaplan-Meier survival curve. Median OS (95% CI), 95.000 (26.545-163.455).

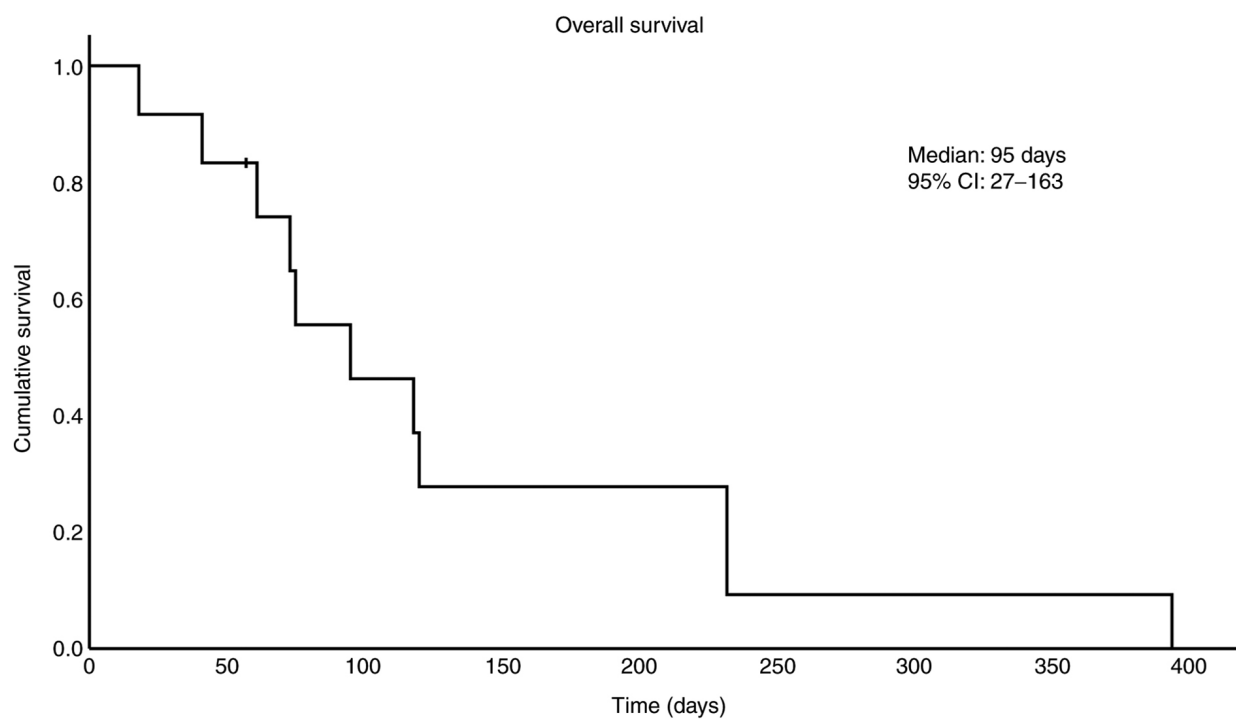


Table SI. Study selection criteria.

Inclusion criteria	<ul style="list-style-type: none"> <li>•Diagnosis of relapsed or refractory non M3-AML or newly diagnosed non M3-AML patients who are not eligible for or unwilling to undergo intensive induction chemotherapy.</li> <li>•ECOG PS &lt;2.</li> <li>•Life expectancy &gt;3 months.</li> <li>•Adequate renal, hepatic and cardiac functions (defined as: Serum creatinine &lt;2X ULN or CrCl &gt;40 ml/min; bilirubin &lt;2X ULN; ALT and AST &lt;2.5X ULN).</li> <li>•LVEF &gt;50%.</li> <li>•NYHA CHF: Class II or better.</li> <li>•A highest sensitivity (higher 70% of the samples analyzed) in the bone marrow analysis of the OPB-111077 <i>ex vivo</i> sensitivity test.</li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>•Medical history of other malignancies.</li> <li>•Diagnosis of M3/APL leukemia.</li> <li>•Any systemic antineoplastic therapy received within 14 days before study entry.</li> <li>•Any investigational drug within 28 days before the first dose of study treatment.</li> </ul>

AML, acute myeloid leukemia; M3/APL, acute promyelocytic leukemia; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ULN, upper limit of normal; CrCl, creatinine clearance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CHF, congestive heart failure.

Table SII. Patient characteristics.

Parameter	Total (n=36)	Enrolled patients (n=12)	Screening failure (n=24)	P-value <sup>a</sup>
Age, years, median (range)	67 (26-80)	76 (72-79)	63.4 (26-80)	
Sex n (%)				0.42
Male	25 (69.4)	11 (91.7)	14 (58.3)	
Female	11 (30.6)	1 (8.3)	10 (41.7)	
ECOG PS				0.57
0	14 (38.8)	5 (41.7)	9 (37.5)	
1	18 (50.0)	6 (50.0)	12 (50.0)	
2	2 (5.5)	0 (0)	2 (8.3)	
Unknown	2 (5.5)	1 (8.3)	1 (4.2)	
FLT3-ITD, n (%)				0.297
Not mutated	29 (80.5)	8 (66.7)	21 (87.5)	
Mutated	3 (8.3)	2 (16.7)	1 (4.2)	
Unknown	4 (11.1)	2 (16.7)	2 (8.3)	
NPM1, n (%)				0.002
Not mutated	26 (72.2)	4 (33.3)	22 (91.7)	
Mutated	2 (5.5)	2 (16.7)	0 (0)	
Unknown	8 (2.2)	2 (16.7)	2 (8.3)	
Number of previous lines, n (%)				0.079
1	9 (25)	1 (8.3)	8 (33.3)	
2	15 (41.7)	7 (58.3)	8 (33.3)	
3	8 (22.2)	2 (16.7)	6 (25.0)	
4	1 (2.8)	0 (0)	1 (4.2)	
5	1 (2.8)	1 (8.3)	0 (0)	
6	1 (2.8)	1 (8.3)	0 (0)	
Unknown	1 (2.8)	0 (0)	1 (4.2)	

<sup>a</sup>Data were analyzed using the Chi-square test. ECOG PS, Eastern Cooperative Oncology Group Performance Status; FLT3-ITD, FMS-like tyrosine kinase 3, internal tandem duplication; NPM, nucleophosmin.