Statistical methods

OS, CIR, NRM, and PFS were analyzed using actuarial estimates and the Kaplan-Meier method. The event for OS consisted of death from any cause, and the patients were censored at the date of last contact. The events for PFS were death in remission and relapse. The cumulative risks of relapse and NRM over time were calculated as competing risks with actuarial methods, whereas patients alive and continuing in complete response 1 (CR1) were censored at the date of last contact. The starting point of all survival curves is the date of transplantation, if not stated otherwise. All *P* values were based on log-rank tests.

Results

Patient and transplant characteristics

A total of 140 (very) poor-risk patients with AML were registered in this study during induction chemotherapy for AML or myelodysplasia syndrome; 110 patients underwent an allo-HSCT according to protocol, with either a matched sibling or a matched unrelated donor. The diagnosis of poor-prognosis AML was revised in 1 patient after registration. As a result, this patient was removed from all additional analyses. The reason for exclusion of the remaining 29 patients included refractory AML (n = 8), no sibling or unrelated donor available (n = 7), refusal (n = 4), death (n = 3), and other (n = 7). Patient characteristics are presented in Table 1. Median age at diagnosis was 59 years (range, 18-71). World Health Organization (WHO) performance status was 0 to 1 in 92 patients. Thirty-five patients were refractory to the first cycle of chemotherapy. Of them, 31 and 4 patients achieved CR and partial response, respectively, upon the second cycle of induction chemotherapy. According to the HOVON/SAKK (Swiss Group for Clinical Cancer Research) risk classification (supplemental Appendix, details of the HOVON 116 study, section 1), 77 patients were classified as very poor risk. Transplant characteristics are depicted in Table 2. All patients received 2 cycles of induction chemotherapy. The median time from evaluation of the second cycle to allo-HSCT was 16 days (range, 1-66),

and the median time from diagnosis to allo-HSCT was 110 days (range, 56-205). Forty-one patients received a graft from a matched sibling donor, 61 from a fully matched unrelated donor, and 8 from a mismatched unrelated donor. One patient received a bone marrow graft from a sibling donor. The median follow-up of patients who lived was 23 months. Sixty-seven patients exhibited an EBMT (European Society for Blood and Marrow Transplantation) score of ≥3 points.[24]

Table 1. Patient characteristics (N = 110)

Characteristics	n	%
Age, y		
Median	59	
Range	18-71	
Sex		
Male	67	61
Female	43	39
WBC before SCT, $\times 10^9$/L		
Median	3.9	
Range	0.10-19.5	
WHO performance status		
0	51	46
1	41	37
2	11	10
Unknown	7	6
Response to induction cycle 1		
CR+Cri	66	61
PR	8	7
Refractory	35	32
Response to cycle 2		
CR+Cri	105	96
PR	4	4
Blasts before SCT, %		
Median	2	
Range	0-10	
MRD*		
Positive	21	28
Negative	53	72
HOVON/SAKK risk group		
Poor	33	30
Very poor	77	70
MK	15	19
EVI1	19	25

CR, complete remission; CRi, complete remission with incomplete hematologic recovery; EVI1, ecotropic viral integration site 1; MK, monosomal karyotype; WBC, white blood cell count; WHO, World Health Organization.
*By multiparameter flow cytometry in 74 patients.

Table 2. Transplant characteristics

Characteristics	n	%
Donor source		
Sibling	41	37
Matched unrelated donor	61	55
Mismatched	8	7
Female donor to male recipient		
No	90	82
Yes	20	18
Stem cell source		
Peripheral blood	109	99
Bone marrow	1	1
PB $CD34^+$, $\times 10^6$/kg		
Median	6.4	
Range	2-14	
CMV serostatus patient/donor		
Negative/negative	36	33
Positive/positive	33	30
Other	41	37
Time diagnosis to allo-HSCT, d		
Median	110	
Range	56-05	
Time start CT2 to allo-HSCT, d		
Median	62	
Range	37-21	
Time evaluation CT2 to allo-HSCT, d		
Median	16	
Range	1-66	
Median follow-up for surviving patients, mo	23	
EBMT risk score		
0	2	2
1	4	3
2	35	32
3	59	54
4	8	7

Data are number of patients, percentage of the entire patient sample (N = 110), unless stated otherwise.
CMV, cytomegalovirus; CT, chemotherapy; EBMT, European Group of Blood and Marrow Transplantation; PB, peripheral blood.

Part 1: feasibility of panobinostat alone and in combination with decitabine

Analyses were performed on data from the first 10 patients in the PNB mono and PNB/DAC10 groups. At interim analysis, 1 of 9 patients in the in PNB mono group experienced DLT. Four of 10 patients receiving PNB/DAC20 experienced DLT, consisting of prolonged cytopenia. Consequently, PNB/DAC20 was not considered feasible. The combination of panobinostat and decitabine was further evaluated in the PNB/DAC10 group (10 mg/m^2 of decitabine). Only 1 DLT was observed in the first 10 patients in the group, again because of prolonged cytopenia. Subsequently, the study was expanded, according to design, by inclusion of another 55 patients in the PNB mono and PNB/DAC10 groups. Of note, in total, 13 patients were included in the PNB/DAC20 group because of ongoing inclusion of patients during the interim analysis (Figure 1).

Part 2: completion of protocol treatment and secondary end points

In the second part of the study, the completion of protocol treatment up to the first DLI and outcome was evaluated. Eighty-seven of 110 patients who underwent transplantation were eligible for epigenetic therapy and received the first cycle (Figure 1). The reasons for withdrawal of the epigenetic drugs were GVHD (n = 11), thrombocytopenia (n = 3), renal dysfunction (n = 3), death (n = 2), disease progression (n = 2), liver dysfunction (n = 1), and start of the first cycle beyond day 35 after allo-HSCT (n = 1). Of 110 patients who received allo-HSCT, 60 (55%) were eligible to receive DLI within 115 days. In total, 63 of 75 (84%) patients who received a second cycle of epigenetic therapy received their first planned DLI. Second and third DLIs were given to 40 and 25 patients, respectively. AEs considered to be related to panobinostat and decitabine treatment are shown in Table 3. Epigenetic therapy–related grade 3 and 4 AEs were observed in 23 (26%) of the 87 patients who received epigenetic therapy. Related hematological AEs were noted in only 3 patients, consisting of 1 grade 2 and 2 grade 3 events. In general, panobinostat- and decitabine-related AEs were rapidly reversible after treatment

was interrupted. Of note, AEs were not attributable to either panobinostat or decitabine when the 2 were combined.

Table 3. Number of AEs related to panobinostat and decitabine treatment

	PNB mono (n = 39), n (%)			PNB/DAC20 (n = 13), n (%)			PNB/DAC10 (n = 35), n (%)		
Epigenetic therapy–related toxicity	G2	G3	G4	G2	G3	G4	G2	G3	G4
Blood and bone marrow	1 (2)	0	0	0	2 (13)	0	0	0	0
Gastrointestinal	2 (4)	2 (4)	0	0	0	0	3 (6)	1 (2)	1 (2)
Constitutional symptoms	2 (4)	1 (2)	0	1 (6)	0	0	0	0	0
Infections	3 (7)	0	0	0	0	0	0	0	1 (2)
Metabolic/laboratory	0	1 (2)	1 (2)	0	0	0	0	2 (4)	0
Eye	1 (2)	0	0	0	0	0	0	0	0
Nervous system	0	1 (2)	0	0	0	0	0	1 (2)	0
Skin and subcutaneous tissue	1 (2)	0	0	0	0	0	0	0	0

G, grade.

Figure 2 shows the CIR, NRM, PFS, and OS of all 110 patients who underwent transplantation. The CIR at 24 months was 35% (SE 5), and NRM at 24 months was 16% (SE 4). OS and PFS at 24 months were 50% (SE 5) and 49% (SE 5), respectively. The cumulative incidence of relapse at 24 months in the PNB mono group was 24% (SE 8), and the addition of decitabine did not improve the outcome, with a CIR at 24 months of 46% (SE 9; $P = .29$) in the PNB/DAC10 group (Figure 3). Although not significant, relapse was seen less often in MRD-negative than in MRD-positive patients (CIR at 24 months 35% [SE 7] vs 43% [SE 11], respectively; $P = .09$; supplemental Figure 3). Outcome according to the HOVON risk categories showed an OS of 63% (SE 10) and 46% (SE 6) at 24 months for poor- and very-poor-risk patients with AML, respectively (supplemental Figure 2). As expected, ineligibility for transplantation was associated with a dismal outcome; the overall survival at 12 months was only 19% (SE 8) (supplemental Figure 4).

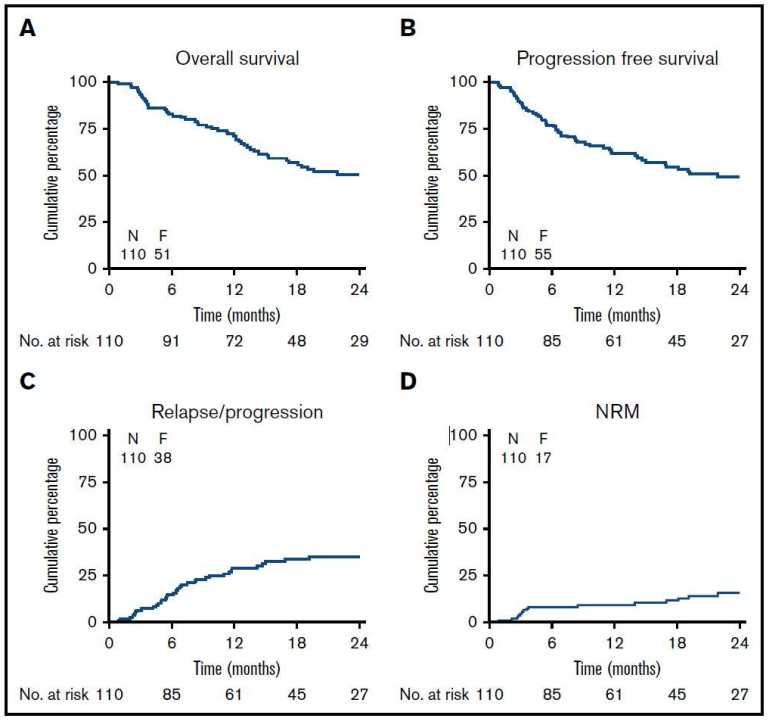

Figure 2. Survival, relapse/progression and NRM. Overall (OS) and progression-free survival (PFS), relapse, and NRM Kaplan-Meier estimates of OD (A), progression-free survival (B), CIR (C), and cumulative incidence of NRM (D). F, number of failures.

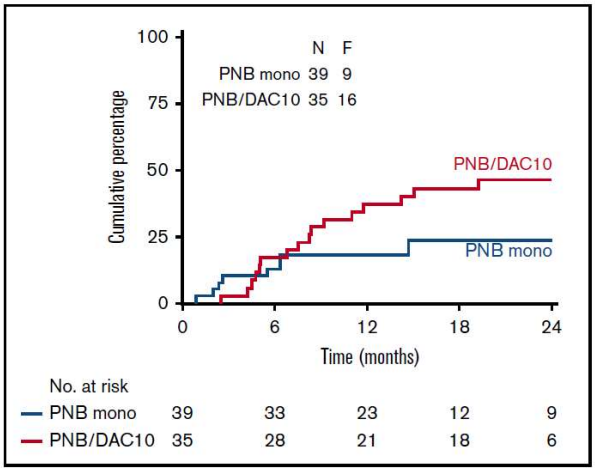

Figure 3. CIR by feasible dose levels in the PNB mono and PNB/DAC10 groups. Kaplan-Meier estimates of CIR in both groups are shown.

Acute GVHD grades 3 and 4 and grades 2 to 4 at 6 months were seen in 5% (SE 2) and 23% (SE 4) of all patients, respectively, and 22% (SE 4) of the patients experienced moderate-to-severe chronic GVHD at 12 months (Figure 4). Of the 110 patients who underwent transplantation, survival was 36% (SE 5); none of the patients experienced relapse or developed acute or chronic GVHD requiring systemic therapy (supplemental Figure 5).

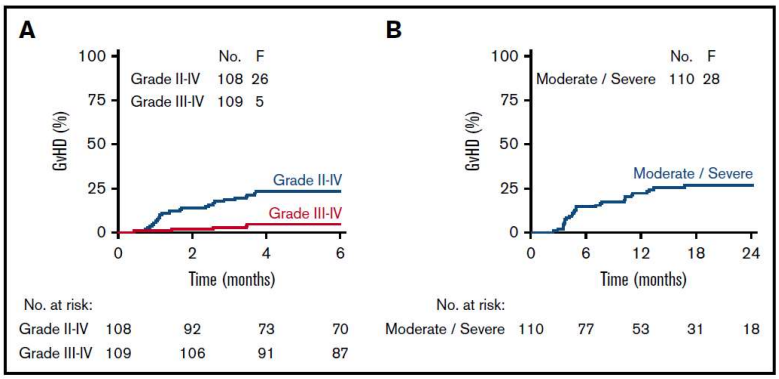

Figure 4. Acute and chronic GVHD. Acute GVHD grades 2 to 4 and grades 3 and 4 (A) and moderate/severe chronic GVHD (B). F, number of failures (ie, acute grades 2 to 4, grades 3 and 4, or moderate/severe chronic GVHD).