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Patients with acute myeloid leukemia (AML), who are refractory to induction therapy or experience relapse after a first complete remission (CR), have an unfavorable prognosis.[1] Epigenetic dysregulation is frequent in AML. In preclinical studies, the pan-deacetylase inhibitor (DACi) panobinostat[2] was shown to modulate the activity of multiple genes in leukemic cell lines,[3] demonstrated single agent activity in AML cell lines and potentiated the activity of doxorubicin in preclinical assays.[4] As a single agent, panobinostat showed modest anti-leukemic activity in early phase clinical trials in advanced hematological malignancies.[5,6] In patients with myeloid disorders 60 mg of panobinostat three times per week (TIW) as single agent in weekly and biweekly schedules was defined as maximally tolerated dose (MTD).

Based on this limited experience, we performed two clinical trials to evaluate the tolerability and clinical efficacy of panobinostat when given as oral monotherapy at the previously established MTD or in combination with intensive chemotherapy for relapsed or refractory (r/r) AML. Panobinostat monotherapy with 60 mg TIW for 28 days (one cycle) was evaluated in a phase II clinical trial following Simon's optimal two-stage design in two strata; A) patients with de novo AML and B) patients with secondary AML. The second study was a phase I study addressing whether panobinostat could be safely combined with Ara-C and mitoxantrone in r/r-AML in escalating doses in adult patients (age $\geq$ 18 years) with r/r AML. In the dose escalation part, oral doses of panobinostat (20 mg, 30 mg, 40 mg, 50 mg, and 60 mg, TIW) were given with fixed dose Ara-C (0.5 g/m^2 IV twice daily, days 1-6) and mitoxantrone (5 mg/m^2 IV, days 1-5) for three, 28-day cycles. Patients with CR or CRi were eligible for maintenance therapy with oral single agent panobinostat at 60 mg TIW. An adaptive Bayesian logistic regression model for combination therapy, including the escalation with overdose control principle, was used to guide the dose escalation of panobinostat.[7] The MTD was determined by dose limiting toxicities (DLTs) in patients who had taken sufficient study drug (at least 5 doses of panobinostat in cycle 1) and had sufficient safety evaluations or discontinued due to DLT in cycle 1. Adverse events (AEs) were evaluated throughout both studies according to the common terminology criteria for adverse events (CTCAE), version 3.0[9]. Response was evaluated according to Cheson's criteria,[10] based on investigator's assessment of response.

In the Monotherapy study 59 patients with a median age of 66 years (range, 27-84) were enrolled, 32 in Stratum A and 27 in Stratum B. Baseline characteristics are shown in Table 1A. All patients discontinued the study (Table 2), primarily for disease progression (24, 40.7%), AEs (19, 32.2%) and death (6, 10.2%). Fifteen patients (25.4%) entered post-treatment evaluation after 6 cycles of therapy and continued to be followed after treatment ended. Overall, 43 patients (72.9%) were exposed to panobinostat for < 8 weeks, the median overall exposure was 33 days. The median cumulative dose of panobinostat was 600 mg; Stratum A = 652.5 mg and Stratum B = 600 mg. The median dose intensity of panobinostat was 22.5

mg/day. The median overall relative dose intensity (RDI) was 85.7%; Stratum A = 80.0% and Stratum B = 100%. All 59 patients treated with panobinostat monotherapy experienced at least one AE, which was suspected to be related to study drug in 53 patients (89.9%). Most common grade ≥ 3 AEs suspected to be related to study treatment were reported in 34 (57.6%) patients. In both strata, the most common all grade AEs suspected to be study drug-related included diarrhea (62.7%), nausea (40.7%), thrombocytopenia (30.5%), decreased appetite (27.1%), and vomiting (23.7%). Overall, 52 patients (88.1%) experienced serious AEs (SAEs), and of these, SAEs were suspected to be study drug-related in 23 patients (38.9%). The most frequent grade ≥ 3 SAEs in both strata included thrombocytopenia (16, 27.1%) and febrile neutropenia (9, 15.3%). Overall, 42 patients died in the study and in the majority of cases, death was due to disease progression; overall survival after 1 and 2 years were 12% and 0%, respectively. For panobinostat monotherapy, the stage 1 review of best response for 26 patients in Stratum A revealed only one patient with a CRi, and for the 26 patients in Stratum B, one CR and one CRi. Therefore, enrollment to study was halted. Based on the final analyses of all enrolled patients, the CRR (CR/CRi) was 3.1% and 7.4% in Stratum A and Stratum B, respectively. All patients who responded had normal cytogenetics.

In the combination therapy study, 59 patients (median age 60 years, range, 19-76) were enrolled into the following panobinostat dosing cohorts: 20 mg (5 patients), 30 mg (8 patients), 40 mg (10 patients), 50 mg (30 patients), and 60 mg (6 patients); baseline characteristics are summarized in Table 1B. The treatment during the dose escalation and dose expansion part of the study was completed as per protocol by 26 patients, while 33 patients discontinued prematurely, mainly due to death (n=11), adverse events (n=8), or disease progression (n=7). Four patients entered the single agent extension part of the study and seven patients proceeded to stem cell transplantation (SCT). The majority of patients (78%) received panobinostat for one treatment cycle, median cumulative dosing was 6 doses, and the median duration of exposure was 12 days, for all dosing cohorts. The relative dose intensity was 1, indicating that the planned dose intensity corresponded to the received dose intensity. A total of 13 patients received 2 cycles of study treatment, and 3 patients in the 50 mg (n=2) and 60 mg (n=1) cohorts received 3 cycles. Of the 59 patients enrolled, 34 were evaluable for MTD determination. A total of 14 DLTs were observed in 6 patients, none in the 20 mg and 30 mg dose groups, in one in the 40 mg group (grade 4 sepsis and grade 3 tachycardia), 2 in the 50 mg group (grade 3 diarrhea, grade 3 QTcF prolongation, grade 3 nausea, grade 3 toxic exanthema, grade 3 vomiting) and 3 in the 60 mg group (grade 4 sepsis, grade 3 neutropenic colitis, grade 3 worsening bilateral pneumonia, grade 3 diarrhea leading to hypokalemia, grade 3 pancytopenia, grade 3 hypokalemia). The MTD was determined to be 50 mg panobinostat in the study dosing schedule. The chance of either excessive or unacceptable toxicity at this MTD dose was calculated to be 5.9% (i.e., < 25%), while for 60 mg panobinostat, this was calculated to be 34.4% (i.e., ≥ 25%). All 59 patients treated with panobinostat combination therapy experienced at least one AE that was suspected to be

related to study treatment in 93% of patients, and in 88% of the patients this was a grade ≥ 3 AE. Most common grade ≥ 3 non-hematologic AEs suspected to be related to study treatment were diarrhea (20%), nausea (5%), vomiting (5%), hypokalemia (7%), and sepsis (5%). Adverse events led to study discontinuation in 19 patients (32%), and in 6 (10%) of these patients discontinuation was due to an SAE considered to be related to study treatment. The most frequent AEs leading to discontinuation were sepsis including septic shock and fungal sepsis (7 events), QT prolongation and hypokalemia (2 events each). Eleven patients (19%) died during or within 28 days of completing treatment. Causes of deaths were sepsis (n=5) septic shock (n=2), fungal infection (n=1), candidiasis (n=1), acute respiratory distress syndrome (n=1) and intracranial hemorrhage (n=1). By investigator assessment, the overall response rate with the combination therapy was 56% (CR in 18 patients [31%], CRi in 9 patients [15%], and PR in 6 patients [10%]). The response rate at the MTD (50 mg) was 50%, (CR, 20% plus CRi, 23% plus PR, 7%). Responses were seen at all dose levels of panobinostat without a clear evidence of dose response relationship (Table 3). Responses were seen exclusively in patients with ELN 2010 favorable or intermediate-1 risk group as well as in patients with a first CR > 6months. Taken together at the previously reported MTD dose of 60mg for single agent therapy, panobinostat was efficacious only in single cases and was poorly tolerated in patients with r/r-AML. Other DACi's such as vorinostat,[11] belinostat,[12] and entinostat[13] also showed poor efficacy in AML when used as a single agent. MTD of panobinostat in combination with mitoxantrone and cytarabine was found to be 50 mg thrice weekly, which was comparable to the MTD of 60 mg determined for single agent panobinostat. The addition of panobinostat did not significantly increase the rate of AEs. In two other studies[14] evaluating panobinostat in combination with idarubicin and cytarabine within a standard 7+3 induction therapy the identified MTD was considerably lower (10mg and 20mg, respectively) suggesting a relevant drug-drug interaction between panobinostat and idarubicin that is not relevant in combination with mitoxantrone. A CR/CRi rate in the combination therapy study of 46% and an overall survival rate of 15% at 4 years do not indicate promising efficacy.[1]

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Table 1A. Baseline patient demographics and disease characteristics for all patients enrolled in panobinostat monotherapy trial

Demographic variable	Monotherapy Trial Panobinostat Dose =60 mg		
n (%)	**Stratum A (n=32)**	**Stratum B (n=27)**	**Total (N = 59)**
Sex - Male	12 (37.5)	19 (70.4)	31 (52.5)
Age (years) Median (range)	63 (27-83)	68 (49-84)	66 (27-84)
Age Category <65 years	18 (56.3)	8 (29.6)	26 (44.1)
≥ 65 years	14 (43.8)	19 (70.4)	33 (55.9)
ECOG PS PS = 0	11 (34.4)	5 (18.5)	16 (27.1)
PS = 1	14 (43.8)	17 (63.0)	31 (52.5)
PS = 2	7 (21.9)	5 (18.5)	12 (20.3)
	Disease Status		
De Novo AML	32 (100)	0	32 (54.2)
Secondary to MDS	0	23 (85.2)	23 (39.0)
Secondary to AHD	0	4 (14.8)	4 (6.8)
Refractory to initial induction	13 (40.6)	15 (55.6)	28 (47.5)
Relapsed	18 (56.3)	12 (44.4)	30 (50.8)
	Duration of Initial Response		
≤ 6 months	11 (34.4)	10 (37.0)	21 (35.6)
> 6 to ≤ 12 months	10 (31.3)	5 (18.5)	15 (25.4)
> 12 months	11 (34.4)	12 (44.4)	23 (39.0)

ECOG PS: Eastern cooperative oncology group, performance status; MDS: myelodysplastic syndrome; AHD: antecedent hematopoietic disorder, Stratum A: refractory de novo AML, Stratum B: refractory AML secondary to MDS/AHD

Table 1B. Baseline patient demographics and disease characteristics for all patients enrolled in Combination trial

Demographic variable	Combination Trial Panobinostat Doses					
n (%)	**20 mg (n = 5)**	**30 mg (n = 8)**	**40 mg (n = 10)**	**50 mg (n = 30)**	**60 mg (n = 6)**	**Total (N = 59)**
Sex - Male	4 (80.0)	6 (75.0)	5 (50.0)	16 (53.3)	2 (33.3)	33 (55.9)
Age (years) Median (range)	53 (19-72)	52 (35-70)	54 (22-68)	60.5 (26-76)	66 (60-73)	60 (19-76)
Age Category <65 years	3 (60.0)	5 (62.5)	8 (80.0)	20 (66.7)	3 (50.0)	39 (66.1)
≥ 65 years	2 (40.0)	3 (37.5)	2 (20.0)	10 (33.3)	3 (50.0)	20 (33.9)
ECOG PS PS = 0	4 (80.0)	3 (37.5)	7 (70.0)	11 (36.7)	3 (50.0)	28 (47.5)
PS = 1	1 (20.0)	5 (62.5)	2 (20.0)	18 (60.0)	2 (33.3)	28 (47.5)
PS = 2	0	0	1 (10.0)	1 (3.3)	1 (16.7)	3 (5.1)
	Disease Status					
Primary refractory AML	1 (20.0)	4 (50.0)	1 (10.0)	9 (30.0)	2 (33.3)	17 (28.8)
Relapse: first	4 (80.0)	4 (50.0)	9 (90.0)	21 (70.0)	4 (66.7)	42 (71.2)
	Duration of Initial Response					
≤ 6 months	0	3 (37.5)	2 (20.0)	9 (30.0)	0	14 (23.7)
> 6 to ≤ 12 months	2 (40.0)	0	1 (10.0)	9 (30.0)	0	12 (20.3)
> 12 months	2 (40.0)	3 (37.5)	5 (50.0)	3 (10.0)	4 (66.7)	17 (28.8)
unknown	1 (20.0)	2 (25.0)	2 (20.0)	9 (30.0)	2 (33.3)	16 (27.1)
	Cytogenetic Risk Category (ELN 2010)					
Favorable	2 (40.0)	0	4 (40.0)	5 (16.7)	1 (16.7)	12 (20.3)
Intermediate-1	1 (20.0)	0	3 (30.0)	8 (26.7)	1 (16.7)	13 (22.0)
Intermediate-2	1 (20.0)	2 (25.0)	0	8 (26.7)	1 (16.7)	12 (20.3)
Unfavorable	1 (20.0)	3 (37.5)	3 (30.0)	1 (3.3)	1 (16.7)	9 (15.3)
Unknown	0	3 (37.5)	0	8 (26.70	2 (33.3)	13 (22.0)

Table 2. Patient disposition for monotherapy and combination trials, Primary reason for end of treatment

Patient Disposition	Monotherapy Trial Panobinostat Dose 60 mg/d TIW			Combination Trial Panobinostat doses					
	Stratum A(n=32)	Stratum B(n=27)	Total (N=59)	20 mg (n=5)	30 mg (n=8)	40 mg (n=10)	50 mg (n=30)	60 mg (n=6)	Total N = 59
Enrolled (treated)	32 (100)	27 (100)	59 (100)	5 (100)	8 (100)	10 (100)	30 (100)	6 (100)	59 (100)
Discontinued	32 (100)	27 (100)	59 (100)	5 (100)	8 (100)	10 (100)	30 (100)	6 (100)	59 (100)
	Primary reason for end of treatment			**Primary reason for end of treatment**					
Completed per protocol				0	2 (25.0)	4 (40.0)	17 (56.7)	3 (50.0)	26 (44.1)
Death	4 (12.5)	2 (7.4)	6 (10.2)	0	1 (12.5)	2 (20.0)	7* (23.3)	1 (16.7)	11 (18.6)
Adverse event(s)	10 (31.3)	9 (33.3)	19 (32.2)	1 (20.0)	1 (12.5)	2 (20.0)	2 (6.7)	2 (33.3)	8 (13.6)
Disease progression	13 (40.6)	11 (40.7)	24 (40.7)	3 (60.0)	0	1 (10.0)	3 (10.0)	0	7 (11.9)
Withdrew consent	3 (9.4)	4 (14.6)	7 (11.9)	0	2 (25.0)	1 (10.0)	0	0	3 (5.1)
Other reasons†	2 (6.3)	1 (3.7)	3 (5.1)	1 (20.0)	2 (25.5)	0	1(3.3)	0	4 (6.7)
	Entered post treatment evaluation			**Entered extension part of the study**					
	10 (31.1)	5 (18.5)	15 (25.4)	1 (20.0)	1 (12.5)	2 (20.0)	0	0	4 (6.8)
				Proceeded to stem cell transplant					
	Unknown			0	2 (25.0)	1 (10.0)	4 (13.3)	0	7 (11.9)

*One patient stopped treatment due to AEs, but died of disease progression a few days after the end of treatment. This patient is counted as a part of total deaths during the combination trial.
†For single agent trial other reasons for end of treatment include lost to follow up, protocol deviation and new cancer therapy. For combination trial other reasons for end of treatment include administrative issues, and abnormal test procedure results.

Table 3. Best overall response as per investigator assessment for the combination trial, by initial dose group of panobinostat

	Panobinostat doses					
Best overall response	**20 mg**	**30 mg**	**40 mg**	**50 mg**	**60 mg**	**Total**
	N = 5	**N = 8**	**N = 10**	**N = 30**	**N = 6**	**N = 59**
Complete remission (CR)	2 (40.0)	1 (12.5)	5 (50.0)	6 (20.0)	4 (66.7)	18 (30.5)
Morphologic CR with incomplete blood count recovery (CRi)	0	1 (12.5)	0	7 (23.3)	1 (16.7)	9 (15.3)
Partial remission (PR)	0	3 (37.5)	1 (10.0)	2 (6.7)	0	6 (10.2)
Treatment failure	3 (60.0)	2 (25.0)	1 (10.0)	9 (30.0)	0	15 (25.4)
Unknown	0	1 (12.5)	3 (30.0)	6 (20.0)	1 (16.7)	11 (18.6)
Rate of CR or CRi or PR	2 (40.0)	5 (62.5)	6 (60.0)	15 (50.0)	5 (83.3)	33 (55.9)
95% confidence interval (CI)	5.3, 85.3	24.5, 91.5	26.2, 87.8	31.3, 68.7	35.9, 99.6	42.4, 68.8
Time to remission (days) Median (95% CI)	114 (22, 114)	32.5 (21, 99)	25 (22, 54)	42 (25, 88)	43 (23, 126)	42 (25, 54)

PR: partial remission, CR: complete remission; CRi: complete remission with incomplete blood recovery; CI: confidence interval.