Title:A Phase 1b/2b Multicenter Study of Oral Panobinostat Plus Azacitidine in AdultsWith MDS, CMML, or AMLWith < 30% Blasts

Short Running Title: Panobinostat Plus Azacitidine in MDS, CMML, or AML

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Key Points:

- The addition of panobinostat to azacitidine increased composite complete responses but not median overall survival or timetoprogression.
- Further dose or schedule optimization is warranted to improve the risk/benefit profile of panobinostat in combination with azacitidine.

Abstract

Treatment with azacitidine (AZA), a demethylating agent, significantly prolonged median overall survival vs conventional care in patients with higher-risk myelodysplastic syndromes (MDS). As median survival with monotherapy is <2 years, novel agents are needed that further improve outcomes. Preclinically, the potent pan-deacetylase inhibitor panobinostat(PAN) acted synergistically with demethylating agents. This phase 1b/2b trial (n = 113 patients) was designed to determine maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of PAN+AZA (phase 1b) and to evaluate early efficacy and safety of PAN+AZAvsAZAmonotherapy(phase 2b) in patients with higher-risk MDS, chronic myelomonocytic leukemia (CMML), or oligoblastic acute myeloid leukemia (AML) with < 30% blasts. The MTD was not reached; the RP2D was determined to be PAN30 mg plusAZA 75 mg/m^2. In phase 2b, a higher proportion of patients in the PAN+AZA arm achieved a composite complete response (complete response + morphologic complete response with incomplete blood count + bone marrow complete response (27.5% [95% CI, 14.6%-43.9%]) compared with AZA alone (14.3% [95% CI, 5.4%-28.5%]). However, no significant difference was observed in overall survival (1-year survival rate: PAN+AZA 60% [95% CI, 50%-80%]; AZA 70% [95% CI, 50%-80%]) or timetoprogression (probability at 12 months: PAN+AZA 70% [95% CI, 40%-90%]; AZA 70% [95% CI, 40%-80%]). Additionally, there were higher rates of grade 3/4 adverse

events (97.4% vs 81.0%) and on-treatment deaths (13.2% vs 4.8%) in the PAN+AZA arm. Further dose or schedule optimization is warranted to improve the risk/benefit profile of this regimen.

Introduction

Myelodysplastic syndromes (MDS) represent a heterogeneous group of myeloid disorders characterized by severe cytopenias and dysplasias in one or more myeloid lineages. Subclassification of MDS according to several prognostic scoring systems identifies patients at substantial risk for transformation to acute myeloid leukemia (AML) that is generally refractory to standard treatment.[1] MDS remains incurable without stemcell transplant, but the advanced age of patients restricts the number eligible for such therapy.[2] Azacitidine (AZA), the current standard, front-line therapyfor higher-risk MDS, significantly prolonged overall survival (OS) in these patients and has shown clinical benefit in those with AML.[3-5] However, response rates with AZA therapy are, in general, < 30%[6,7] and of limited durability, with all nontransplanted patients eventually progressing or dying, highlighting the significant need for novel agents with the potential to improve both response rates and duration of responses.

Panobinostat (PAN) is a potent pan-deacetylase inhibitor (DACi) recently approved in the United States for patients with multiple myeloma.[8]PAN modulates the acetylation of histone proteins and protein chaperones in malignant cells. The epigenetic regulation by PAN is primarily mediated through the inhibition of class I histone deacetylase enzymes leading to increased histone acetylation, relaxation of chromatin, and alteration of gene expression, including that of tumor suppressor genes.[9] In a phase 1a/2 study of oral PAN in patients with advanced hematologic malignancies, a manageable safety profile was established, but only modest efficacy was demonstrated in patients with AML or MDS.[10]

In recent years, the involvement of epigenetic processes in the pathogenesis of MDS and the transformation to AML has been extensively studied. Several preclinical and clinical studies have demonstrated hypermethylation of CpG islands at the promoter regions of a number of genes.[11] Additionally, epigenetic silencing of tumor suppressor genes in MDS, potentially mediated through dysregulated histone acetylation, has been associated with transformation to AML and poor

prognosis.[12]That both AZA and DACi modulate aberrant gene expression by different mechanisms suggests that they may act synergistically in MDS and AML. A limited number of clinical trials investigating the combination of DACi and demethylating agents have been fully reported, but early-phase clinical trials of the combination of AZA and a number of DACi's have shown promising response rates.[13-16] As PAN is among the most potent DACi in clinical development,[17] we hypothesized that the combination of PAN and AZA could show clinical benefitover AZA monotherapy. Preclinically, synergy of PAN and demethylating agents has been established in primary AML cells, with the combination of PAN and decitabine leading to a significant reduction in AML cell viability compared with either agent alone.[18]

On the basis of these data, the current phase 1b/2b study was designed to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D), and the early efficacy and safety, of PAN in combination with AZA in patients with high-risk MDS, oligoblastic AML, or chronic myelomonocytic leukemia (CMML).

Methods

Patients

Adult patients (aged ≥ 18 years) with International Prognostic Scoring System (IPSS) intermediate-2 or high-risk MDS, CMML, or AML with multilineage dysplasia and ≤ 30% bone marrow blasts who were not planning to undergo hematopoietic stem cell transplant were enrolled. Key inclusion criteria were an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2 and adequate hepatic and renal function. Patients with therapy-related MDS or AML, relapsed/refractory AML, clinical symptoms of central nervous system leukemia, or impaired cardiac function were excluded. Additionally, patients who had received prior treatment with a DACi, AZA, or decitabine, or who were currently receiving a drug known to prolong the QT interval that could not be terminated, were not eligible. The study protocol was reviewed by theindependent ethics committee or institutional review board at each

center, and written informed consent was obtained from each patient prior to any screening procedures.

Study Design

This was an open-label, multicenter international phase 1b/2b study. In phase 1b, the primary objective was determination of the MTD or RP2D of PAN in combination with AZA (Figure 1). Other objectives included early analyses of the safety and efficacy of the regimen. Patients were enrolled in escalating dose cohorts consisting of ≥ 3 patients each. The starting dose of PAN was 20 mg administered orally on days 3, 5, 8, 10, 12, and 15 in combination with AZA75 mg/m^2administered on days 1 to 7 in 4-week cycles. Successive cohorts received escalating doses of PAN until determination of MTD or RP2D. Dose reductions or interruptions were permitted, but the PAN dose was not to decrease below 10 mg. Patients were evaluated for dose-limiting toxicities (DLTs), and dose escalation was guided by an adaptive Bayesian logistic regression model (BLRM). The MTD could not be declared until ≥ 9 patients were evaluated at the dose level in question.

Upon determination of the MTD or RP2D defined in phase 1b, an additional 80 patients were to be enrolled in the phase 2b portion and randomly assigned in a 1:1 ratio to receive either the MTD/RP2D of PAN plus AZA (PAN+AZA) or single-agent AZA on a treatment schedule identical to that from phase 1b. The primary objective of phase 2b was to assess the early efficacy of PAN at the MTD/RP2D in combination with AZA vs AZA alone through the assessment of composite complete response (complete response [CR] + morphologic complete response with incomplete blood count [CRi] + bone marrow complete response [BM-CR]). Secondary objectives included efficacy assessment of clinical responses other than composite CR, 1-year survival, time to progression, and assessment of safety in comparison with single-agent AZA.[19,20] Patients in both phases were allowed to continue study treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

Safety and Efficacy Assessments

Patients were monitored for safety throughout the trial and up to 28 days after the last dose of study treatment. Adverse events (AE) were assessed according to the Common Terminology Criteria for Adverse Events version 3.0. Safety evaluations included monitoring of hematology, blood chemistry, and urine, and regular assessment of vital signs, physical condition, body weight, ECOG PS, and cardiac monitoring.

Assessment of response to therapy was made per the investigator, based on standardized criteria proposed by the international working groups for AML[19] and for MDS and CMML.[20] Response during study treatment was evaluated via blood and bone marrow assessment. Bone marrow aspiration and/or core biopsy was obtained within 5 days of the planned end of even-numbered cycles, at the end of treatment visit, and at the discretion of the investigator. Peripheral blood assessments were performed within 5 days of bone marrow aspiration/biopsy, unless not clinically feasible.

Bone marrow aspirate samples were collected at screening from patients in phase 2b and sent for next-generation sequencing analysis (NGS; Genoptix, Carlsbad, CA). Genomic DNA was isolated from the samples, and the coding regions of 24 genes (Supplementary Table 1) were amplified by polymerase chain reaction and sequenced using NGS technology (MiSeq system; Illumina, Inc, San Diego, CA). Somatic mutations consistent with AML, MDS, or myeloproliferative neoplasms were identified.This study is registered at http://clinicaltrials.gov as NCT00946647.

Statistical Analysis

An adaptive BLRM and dose-escalation criteriasimilar to that proposed by Babb, Rogatko, and Zacks, including the escalation with overdose control principle,[21] was used to guide dose escalation in phase 1b. The study was not designed for hypothesis testing of comparisons between the treatment arms. Point estimates and 95% exact binomial CIs[22] were computed to provide descriptive summaries of

response rates. The 1-year survival probabilities were estimated from the Kaplan-Meier curve. All analyses were done using SAS software (version 9.3) and R software (version 2.13).

Results

Patients and Disposition

A total of 113 patients were enrolled in the study with a data cutoff for this analysis of April 30, 2014. In phase 1b, 31 patients (median age, 69 years; Table 1) receivedPANin dosing cohorts of 20 mg (n=6), 30 mg (n=18), and 40 mg (n=7). At the time of data cutoff, 4 patients remained on treatment (30 mg [n=3]; 40 mg [n=1]). Patients in phase 1b had diagnoses of MDS (n=16), CMML (n=4), and AML (n=11). The majority of patients with MDS were previously untreated (81.3%), categorized as IPSS intermediate-2 (87.5%) or high risk (12.5%) at study entry, and had favorable cytogenetics per IPSS (62.5%); 12.5% had unfavorable cytogenetics. Among the patients with CMML, 75% were previously untreated. All patients with AML were previously untreated for AML; 72.7% had prior MDS that transformed to AML, and 1 of these patients received prior treatment with lenalidomide for MDS. A majority of patients with AML(54.5%) had unfavorable cytogenetics; the remaining 45.5% had intermediate cytogenetic risk. The median time from initial diagnosis to study entry for patients with MDS, CMML, and AML was 1.3 months (range, 0.5-37.9 months), 1.8 months (range, 0.8-3.2 months), and 0.7 months (range, 0.2-2.5 months), respectively. Most patients had an initial ECOG PS of either 0 (41.9%) or 1 (48.4%). A summary of demographics and baseline characteristics for patients in phase 1b is presented in Table 1.

A total of 82 patients (median age, 71 years) were enrolled in phase 2b and randomized to receive treatment with PAN+AZA (n=40) or AZA (n=42). At the time of data cutoff, 13 patients remained on treatment (PAN+AZA [n=7]; AZA [n=6]). Of the 82 phase 2b patients, 47 (57.3%), 13 (15.9%), and 22 (26.8%) had a diagnosis of MDS, CMML, and AML, respectively. The majority of patients with MDS were previously untreated (89.4%), and 44.7% had unfavorable cytogenetics (patients with favorable and

intermediate cytogenetics accounted for 27.7% each). Patients with CMML were primarily untreated (84.6%), andnearly all patients with AML (95.5%) were previously untreated for AML. Most patients with AML had multilineage dysplasia with 21% to 30% bone marrow blasts (95.5%), with 77.3% of these patients having prior MDS that transformed to AML and most (81.8%) having intermediate or high cytogenetic risk. ECOG PS at baseline was primarily 0 (41.5%) or 1 (52.4%). A comparison of demographics and baseline characteristics between treatment arms is presented in Table 2.

Determination of MTD or RP2D

Of the 31 patients enrolled in phase 1b, 26 were evaluable for MTD determination (20 mg: 5; 30 mg: 14; 40 mg: 7). A total of 6 DLTs were observed. In the 20-mg cohort, 1 patient experienced a DLT (not specified). Three patients in the 30-mg cohort experienced DLTs, which included atrial fibrillation and syncope, dehydration and fatigue, and colitis. In the 40-mg cohort, 2 patients experienced DLTs of grade 3 nausea and vomiting and grade 3 hyperbilirubinemia. The MTD for PAN was not reached. Although DLTs were rare, 2 patients (29%) required at least one PAN dose reduction and 1 patient (14%) required at least one AZA dose reduction. Based on the BLRM and safety findings, the 30-mg dose was selected as the RP2D.

Safety

During phase 1bdose escalation, nearly all patients (96.8%) reported at least one grade 3/4 AE, regardless of study drug relationship. The most common grade 3/4 AEs (in ≥20% of patients) were primarily hematologic, including thrombocytopenia (54.8%), neutropenia (41.9%), anemia (32.3%), and febrile neutropenia (29.0%; Table 3). Twenty-one patients(67.7%) required at least onePANdose reduction or interruption with no apparent relationship between PAN dose level and frequency of dose delay/change, and 17 patients (54.8%) required at least oneAZA dose reduction or interruption. AEs led to treatment discontinuation in 38.7% of patients, with febrile neutropenia (6.5%) and atrial fibrillation

(6.5%) reported as the most common AEs leading to discontinuation of treatment. Three patients (9.7%) died while on treatment (or within 28 days after the end of treatment) from underlying malignancy (n=2) and renal insufficiency not attributed to study drug treatment(n=1).

In phase 2b, a total of 80 randomized patients (38 PAN+AZA; 42 AZA) received at least one dose of study treatment and were included in the safety set. The median duration of treatment with PANwas 20.5 weeks and for AZA was 23.4 weeks in the PAN+AZA arm vs 16.9 weeks in the AZAarm. A summary of frequent AEs by treatment group in phase 2b is presented in Table 4. A greater proportion of patients in the PAN+AZA arm experienced at least one grade 3/4 AE compared with the AZAarm (97.4% vs 81.0%). The most common grade 3/4 AEs with higher incidence in the PAN+AZA arm than the AZA arm were thrombocytopenia (55.3% vs 19.0%), febrile neutropenia (31.6% vs 19.0%), and anemia (21.1% vs 11.9%)). A slightly higher proportion of patients in the PAN+AZA than in the control arm experienced at least one serious AE (71.1% vs 64.3%), with febrile neutropenia (26.3% vs 14.3%), pneumonia (18.4% vs 9.5%), sepsis (7.9% vs 7.1%), thrombocytopenia (7.9% vs 7.1%), sepsis during neutropenia (0% vs 7.1%), pyrexia (5.3% vs 0%), and septic shock (5.3% vs 0%) being the most common serious AEs reported in > 5% of patientsin either arm. Among patients in the PAN+AZA arm, 78.9% required at least onePAN dose reduction or interruption and 65.8% required reduction of AZA compared with 71.4% in the AZA arm. The most common reasons for PAN dose reduction/interruption were AEs (68.4%) and scheduling conflicts (traveling issues, holidays, illness, etc; 57.9%). In the PAN+AZA arm, a relative dose intensity of ≥ 90% was achieved for PANin only 47.4% of patients and for AZAin 71.1%. In the AZA arm, 73.8% of patients had relative dose intensity ≥ 90%. A greater proportion of patients in the PAN+AZA arm discontinued treatment due to AEs compared with the control arm (36.8% vs 23.8%). The most common AEs leading to treatment discontinuation in the PAN+AZA and AZA arms were febrile neutropenia (5.3% vs 0%), sepsis (5.3% vs 2.4%), and septic shock (5.3% vs 0%), respectively. There was a total of 7 on-treatment deaths (PAN+AZA, n=5 [13.2%]; AZA, n=2 [4.8%]), which all occurred between the first and

third cycles of treatment. None of the patients were known to be in response. In the PAN+AZA arm, 1 patient died due to MDS and 2 patients died due to causes that were suspected by the investigator to be related to study treatment (septic shock during grade 4 febrile neutropenia and pulmonary hemorrhage during grade 4 thrombocytopenia). Neither of the deaths in the AZA arm was suspected to be due to study treatment.

Early Efficacy

Phase 1b

The clinical response rates were 33.0%, 33.0%, and 42.9% in the 20-mg, 30-mg, and 40-mg cohorts, respectively.

Among patients with MDS/CMML across all dose cohorts, a clinical response (CR, BM-CR, partial response [PR], or hematologic improvement [HI]) was observed in 6 patients (30.0%; 95% CI, 11.9%-54.3%), with 2 CRs (10.0%), 2 BM-CRs (10.0%), 1 PR (5.0%), and 1 HI (5.0%). Erythroid and platelet responses were observed in 3 patients (15.0%) each, and no patients had a neutrophil response. Two patients relapsed following HI.

Five patients (45.5%; 95% CI, 16.7%-76.6%) with AML showed a clinical response (CR, CRi, PR), including 2 CRs (18.2%) and 3 CRi's (27.3%). Treatment failure was observed in 3 patients (27.3%), and best overall response was unknown in 3 patients (27.3%). One patient with AML relapsed following CRi.

Phase 2b

A higher proportion of patients achieved a composite CR in the PAN+AZA arm (27.5%; 95% CI, 14.6%-43.9%) vs the AZA arm (14.3%; 95% CI, 5.4%-28.5%), including a slightly higher proportion of patients achieving a CR (15.0% vs 9.5%) or achieving a CRi or BM-CR (12.5% vs 4.8% [Table 5]). However, the

overall response rate (composite CR + PR + HI) was similar across the 2 arms (PAN+AZA, 37.5%; AZA, 38.1%).

For patients with MDS/CMML,the composite CR rate was higher in the PAN+AZA arm vs the control arm (29.0% vs 10.3%; Supplementary Table 2). However, the clinical response (41.9% vs 41.4%), erythroid response (25.8% vs 31.0%), platelet response (35.5% vs 24.1%), and neutrophil response (19.4% vs 13.8%) rates were similar across treatment arms. Relapse was reported in 22.6% of all patients in the PAN+AZA arm vs 17.2% in the AZA arm. Among patients with AML, the clinical response rate was 22.2% (95% CI, 2.8%-60.0%) in the PAN+AZA arm and 30.8% (95% CI, 9.1%-61.4%) in the control arm(Supplementary Table 3).

For the overall phase 2b population, the probability of being progressionfree at 12 months, based on Kaplan-Meier analysis, was similar for both treatment arms (PAN+AZA: 70% [95% CI, 40%-90%]; AZA: 70% [95% CI, 40%-80%]). The 1-year survival, as computed from the Kaplan-Meier analysis of OS, was 60% (95% CI, 50%-80%) in the PAN+AZA arm vs 70% (95% CI, 50%-80%) in the control arm (Figure 2).

Bone marrow aspirate samples from 37 patients (45.1%) were collected for NGS; 20 patients were in the PAN+AZA arm (7 of whom achieved CR) and 17 were in the AZA arm (0 of whom achieved CR). The genes most often mutated in the available samples include *SRSF2* (86.5%), which is involved in RNA splicing; *SETBP1* (75.7%), which plays a role in epigenetics regulation; and *TP53* (51.4%), a tumor suppressor gene (Figure 3). However, there was no clear evidence ofa relationship between mutations and disease status or response.

Discussion

In this study, the combination of PANand AZA did not demonstrate a substantial efficacy benefit compared with AZA alone in patients with higher-risk MDS, CMML, and AML. Additionally, patients in the PAN+AZA arm experienced a higherrate of grade 3/4 AEs. These results were not anticipated based

on the strong preclinical evidence supporting combined treatment with PANand demethylating agents.[18] Similar results were found, though, in phase 2 studies of vorinostat plus AZA for higher-risk MDS and CMML,[23] entinostat plus AZA for MDS and AML,[24] pracinostat plus AZA for previously untreated MDS,[25] and valproic acid plus decitabine for MDS and AML.[26,27]

While we observed improvements in the composite CR rate, the overall response rates were similar between arms, and there was no appreciable benefit in OS with the addition of PAN. One potential reason for the lack of survival benefit in the overall population could be the inherent difficulty in selecting MDS/AML patient populations likely to derive benefit. Currently, there is no good universally acceptedclinical biomarker for response to epigenetic therapy in these indications. A study by Tan et al[28] demonstrated that an elevation of histone H3 and H4 levels of > 50% from baseline following PAN treatment strongly correlated with clinical response.However, a number of other studies examining the correlation between acetylation levels and response have failed to show an association, potentially due to the use of methodology with inherently lower sensitivity.[13,29,30] NGS demonstrated higher rates of *SRSF2* and *SETBP1* mutations than previous studies of similar patient populations,[31-33] and no clear evidence of a relationship between mutations and disease status or response. However, the lack of data for patients in the AZA arm who achieved a CR and the small sample size make it difficult to draw any conclusions.

Consideration should also be given to the potential role of the sequence in which DACi and hypomethylating agents are administered. Although this concept was reflected in scheduling the 2 agents, with PAN started on day 3 of each cycle, both agents were in effect given concurrently for a substantial part of the first week of each cycle. Results from a phase 1 study showed that concurrent administration of vorinostat and decitabine yielded better responses compared with sequential administration[34]; however, PAN has been shown to induce cell cycle arrest,[35] which may lead to

antagonistic effects when used in combination with AZA in the present schedule. Thus, other doses and schedules of this combination may need to be explored.

Furthermore, tolerability of PAN+AZA could potentially have limited the therapeutic efficacy of this combination by preventing delivery of sufficient doses of PANin particular. Only 47.4 % of patients in the combination arm received ≥ 90% of the scheduled dose due to dose reductions and interruptions, which, for the most part, were AErelated. This is one explanation provided for the lack of benefit of AZA plus vorinostat over AZA in the North American Intergroup Study SWOG S1117.[23]Hematologic toxicity is common to both DACi and hypomethylating agents, so the potential for aggravating thrombocytopenia and neutropenia by combining these 2 classes of drugs was anticipated when designing the study. Even though we did not observe extremely prolonged cytopenia attributable to study drugs, hematologic toxicity wasthe principal reason for decreasing drug dose and interrupting or discontinuing treatment. In contrast, gastrointestinal and constitutional AEs were generally well managed and did not constitute a major management problem during the DLT-defining period, so that the number of DLTs in all dose cohorts in phase 1b was below the threshold for declaration of MTD. The overall long-term safety profile of the regimen in this study posed a challenge, with nearly all patients in the PAN+AZA arm of phase 2b (97.3%) reporting at least one grade 3/4 AE vs 81.0% in the AZA arm. Common AEs (≥ 50% in PAN+AZA arm) were nausea, thrombocytopenia, diarrhea, and pyrexia, consistent with the established safety profile of both drugs as singleagents in patients with hematologic malignancies.[6,10,36] Grade 3/4 AEs were primarily managed through dose reduction/interruption, leading to only moderate drug-related discontinuations. However, the observed safety profile was similar to AZA in combination with other, less potent, DACi's.[13,29,37-40] Additionally, in phase 2b, there was a higher rate of on-treatment mortality in the PAN+AZA arm compared with the AZA arm,and the death of 2 of 5 patients in the PAN+AZA arm was suspected by the investigator to be related to study drug treatment.

The anticipation of clinical benefit in the present study was based on compelling preliminary data from an uncontrolled phase 1b/2 trial examining PAN+AZA in patients with higher-risk MDS and AML, which demonstrated an overall response rate of 31% (9/29) for patients with AML and 50% (5/10) for patients with high-risk MDS at the MTD of PAN30 mg plus AZA75 mg/m^2.[28] The observed safety profile was similar to the present study, with high rates of grade 3/4 hematologic AEs including neutropenia (96.2%), thrombocytopenia (91.7%), and anemia (88.9%). As in the previous study, the present trial demonstrated better clinical response in patients with MDS/CMML compared with those with AML. In patients with AML, the addition of PANdid not enhance the clinical benefit of AZA.In patients with MDS/CMML, the composite CR rate was nearly 3 times higher in the PAN+AZA arm (29.0%vs 10.3%).However, as already discussed, there was no OS benefit. There are a number of factors that could have contributed to this. For example, patients may not have stayed on treatment long enough to improve their OS; composite CR may be a poor correlate to OS; the overall response rate, which was similar between the 2 arms, may have a greater influence on OS than composite CR; and the study may have been underpowered for OS.All together, these results suggest that PAN+AZA could provide clinical benefit in select subsets of patients (ie, patients with high-risk MDS); however, further research would be warranted in specific subpopulations.

The results of the present study demonstrate that the regimen of PAN 30 mg plus AZA75 mg/m^2 has an unfavorable risk/benefit profile in patients with MDS, CMML, or AML. The development of a consistent biomarker for patients withMDS/AML likely to respond to DACi could help shift the risk/benefit relationship of this type of regimen. However, in the current therapeutic landscape, further dose and schedule optimization would be warranted to improve the tolerability of the combination in this patient population. It is worth noting that at the time of data cutoff (April 30, 2014), 3 patients from phase 1b and 13 patients from phase 2b (PAN+AZA [n=7]; AZA [n=6]) remained on treatment, with most of the patients having achieved CR.

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Table 1. Demographics and Baseline Characteristics of Patients Enrolled in the Phase 1b Portion by Initial Dose Group of PAN

	PAN+AZA 20 mg n = 6	PAN+AZA 30 mg n = 18	PAN+AZA 40 mg n = 7	All Patients N = 31
Median age (range), years	70 (60-80)	70.5 (57-81)	69 (34-79)	69 (34-81)
Female/male, %	33.3/66.7	55.6/44.4	57.1/42.9	51.6/48.4
Disease, n (%)				
MDS	5 (83.3)	10 (55.6)	1 (14.3)	16 (51.6)
CMML	1 (16.7)	2 (11.1)	1 (14.3)	4 (12.9)
AML	0	6 (33.3)	5 (71.4)	11 (35.5)
ECOG PS, n (%)				
0	2 (33.3)	10 (55.6)	1 (14.3)	13 (41.9)
1	3 (50.0)	7 (38.9)	5 (71.4)	15 (48.4)
2	1 (16.7)	1 (5.6)	1 (14.3)	3 (9.7)

Table 2. Demographics and Baseline Characteristics of Patients Enrolled in the Phase 2b Portion by Treatment Group

	PAN+AZA n = 40	AZA n = 42	All Patients N = 82
Median age (range), years	68 (44-81)	72 (42-85)	71 (42-85)
Female/male, %	27.5/72.5	40.5/59.5	34.1/65.9
Disease, n (%)			
MDS	25 (62.5)	22 (52.4)	47 (57.3)
CMML	6 (15.0)	7 (16.7)	13 (15.9)
AML	9 (22.5)	13 (31.0)	22 (26.8)
ECOG PS, n (%)			
0	14 (35.0)	20 (47.6)	34 (41.5)
1	25 (62.5)	18 (42.9)	43 (52.4)
2	1 (2.5)	4 (9.5)	5 (6.1)

Table 3. Frequent AEs (≥ 20%) Regardless of Study Drug Relationship by Initial Dose Group of PAN in the Phase 1b Portion

	PAN+AZA 20 mg n = 6		PAN+AZA 30 mg n = 18		PAN+AZA 40 mg n = 7		All Patients N = 31	
	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)
Nausea	4 (66.7)	0	14 (77.8)	3 (16.7)	7 (100.0)	1 (14.3)	25 (80.6)	4 (12.9)
Diarrhea	4 (66.7)	1 (16.7)	15 (83.3)	1 (5.6)	4 (57.1)	0	23 (74.2)	2 (6.5)
Fatigue	4 (66.7)	0	13 (72.2)	4 (22.2)	5 (71.4)	0	22 (71.0)	4 (12.9)
Thrombocytopenia	3 (50.0)	2 (33.3)	12 (66.7)	11 (61.1)	5 (71.4)	4 (57.1)	20 (64.5)	17 (54.8)
Vomiting	5 (83.3)	0	9 (50.0)	2 (11.1)	4 (57.1)	1 (14.3)	18 (58.1)	3 (9.7)
Constipation	2 (33.3)	0	11 (61.1)	1 (5.6)	3 (42.9)	0	16 (51.6)	1 (3.2)
Neutropenia	2 (33.3)	2 (33.3)	9 (50.0)	8 (44.4)	3 (42.9)	3 (42.9)	14 (45.2)	13 (41.9)
Decreased appetite	3 (50.0)	0	6 (33.3)	0	5 (71.4)	0	14 (45.2)	0
Anemia	2 (33.3)	1 (16.7)	8 (44.4)	6 (33.3)	3 (42.9)	3 (42.9)	13 (41.9)	10 (32.3)
Pyrexia	2 (33.3)	0	7 (38.9)	1 (5.6)	4 (57.1)	0	13 (41.9)	1 (3.2)
Hypokalemia	1 (16.7)	1 (16.7)	9 (50.0)	4 (22.2)	3 (42.9)	0	13 (41.9)	5 (16.1)
Asthenia	3 (50.0)	1 (16.7)	6 (33.3)	0	3 (42.9)	2 (28.6)	12 (38.7)	3 (9.7)
Hypocalcemia	3 (50.0)	0	7 (38.9)	1 (5.6)	1 (14.3)	0	11 (35.5)	1 (3.2)
Febrile neutropenia	2 (33.3)	2 (33.3)	6 (33.3)	5 (27.8)	2 (28.6)	2 (28.6)	10 (32.3)	9 (29.0)
Blood creatinine increased	1 (16.7)	0	5 (27.8)	0	4 (57.1)	1 (14.3)	10 (32.3)	1 (3.2)
Dyspnea	3 (50.0)	1 (16.7)	5 (27.8)	0	2 (28.6)	1 (14.3)	10 (32.3)	2 (6.5)
Abdominal pain	3 (50.0)	0	5 (27.8)	0	1 (14.3)	0	9 (29.0)	0
Edema peripheral	2 (33.3)	0	4 (22.2)	0	3 (42.9)	0	9 (29.0)	0

Table 4. Frequent AEs (≥ 15%) Regardless of Study Drug Relationship by Treatment Group in the Phase 2b Portion

	PAN+AZA n = 38[a]		AZA n = 42[a]		All Patients N = 80	
	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)	All grades, n (%)	Grades 3/4, n (%)
Nausea	23 (60.5)	4 (10.5)	18 (42.9)	1 (2.4)	41 (51.3)	5 (6.3)
Thrombocytopenia	21 (55.3)	21 (55.3)	11 (26.2)	8 (19.0)	32 (40.0)	29 (36.3)
Diarrhea	19 (50.0)	3 (7.9)	9 (21.4)	1 (2.4)	28 (35.0)	4 (5.0)
Neutropenia	16 (42.1)	16 (42.1)	11 (26.2)	11 (26.2)	27 (33.8)	27 (33.8)
Vomiting	16 (42.1)	3 (7.9)	11 (26.2)	1 (2.4)	27 (33.8)	4 (5.0)
Pyrexia	19 (50.0)	2 (5.3)	8 (19.0)	1 (2.4)	27 (33.8)	3 (3.8)
Anemia	12 (31.6)	8 (21.1)	13 (31.0)	5 (11.9)	25 (31.3)	13 (16.3)
Constipation	10 (26.3)	2 (5.3)	15 (35.7)	0	25 (31.3)	2 (2.5)
Fatigue	8 (21.1)	2 (5.3)	16 (38.1)	0	24 (30.0)	2 (2.5)
Febrile neutropenia	13 (34.2)	12 (31.6)	8 (19.0)	8 (19.0)	21 (26.3)	20 (25.0)
Edema peripheral	8 (21.1)	0	8 (19.0)	0	16 (20.0)	0
Decreased appetite	10 (26.3)	2 (5.3)	6 (14.3)	0	16 (20.0)	2 (2.5)
Asthenia	8 (21.1)	1 (2.6)	6 (14.3)	0	14 (17.5)	1 (1.3)
Pneumonia	8 (21.1)	6 (15.8)	6 (14.3)	5 (11.9)	14 (17.5)	11 (13.8)
Headache	6 (15.8)	0	7 (16.7)	2 (4.8)	13 (16.3)	2 (2.5)
Epistaxis	6 (15.8)	1 (2.6)	6 (14.3)	0	12 (15.0)	1 (1.3)

Hypokalemia	6 (15.8)	4 (10.5)	6 (14.3)	1 (2.4)	12 (15.0)	5 (6.3)
Weight decreased	7 (18.4)	0	4 (9.5)	0	11 (13.8)	0
Cough	6 (15.8)	0	5 (11.9)	0	11 (13.8)	0
Platelet count decreased	7 (18.4)	5 (13.2)	2 (4.8)	2 (4.8)	9 (11.3)	7 (8.8)
Abdominal pain	6 (15.8)	1 (2.6)	1 (2.4)	0	7 (8.8)	1 (1.3)

[a] Two patients enrolled in the AZA arm did not receive medication. In addition, 2 patients enrolled in the PAN+AZA arm received only AZA and were therefore included in the AZA group for analysis.

Table 5. Early Efficacy in the Phase 2b Portion

Best Response	PAN+AZA n = 40	AZA n = 42	All Patients N = 82
Composite CR, n (%) (95% CI)	11 (27.5) (14.6-43.9)	6 (14.3) (5.4-28.5)	17 (20.7) (12.6-31.1)
CR, n (%)	6 (15.0)	4 (9.5)	10 (12.2)
BM-CR (MDS/CMML) or CRi (AML), n (%)	5 (12.5)	2 (4.8)	7 (8.5)
Median time to progression (95% CI), months	NE (11.1-NE)	15.2 (11.0-NE)	NE (12.7-NE)
Median OS (95% CI), months	14.9 (10.4-NE)	15.6 (11.4-NE)	15.4 (13.0-NE)

Abbreviation: NE, not estimable.

Figure Legends

Figure 1. Study design. In phase 1b, patients received escalating doses of PAN in combination with AZA in phase 1b. In phase 2b, patients were randomized to receive treatment with either the RP2D of PAN+AZA or single-agent AZA.

Figure 2. OS analysis. Kaplan-Meier curves are shown for patients randomized to receive PAN+AZA versus AZA alone. Symbols represent censoring times for patients in the PAN+AZA (squares) or AZA (triangles) arms, respectively.

Figure 3. NGS analysis. Patients with NGS data are from phase 2b. A gene is considered to be mutant (MT) if one or more alterations, regardless of functional significance, are detected.

Figure 1.

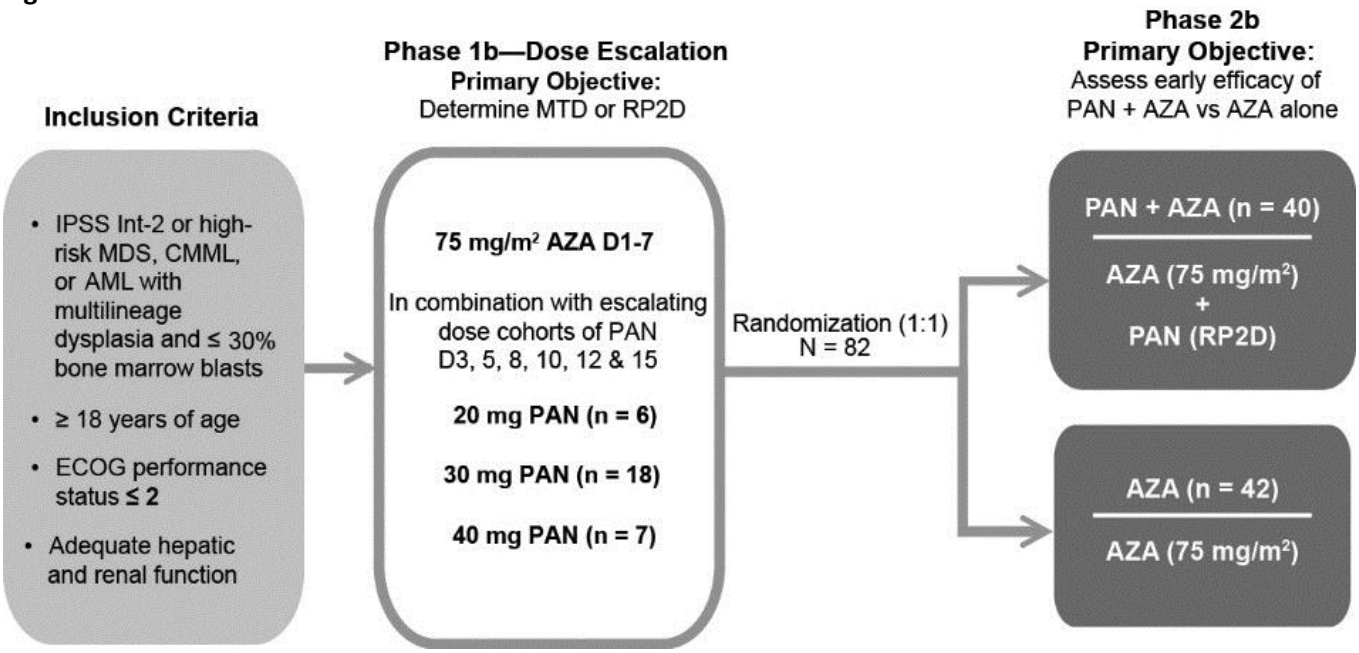

Inclusion Criteria
• IPSS Int-2 or high-risk MDS, CMML, or AML with multilineage dysplasia and ≤ 30% bone marrow blasts
• ≥ 18 years of age
• ECOG performance status ≤ 2
• Adequate hepatic and renal function
Phase 1b—Dose Escalation
Primary Objective:
Determine MTD or RP2D
75 mg/m² AZA D1-7
In combination with escalating dose cohorts of PAN D3, 5, 8, 10, 12 & 15
20 mg PAN (n = 6)
30 mg PAN (n = 18)
40 mg PAN (n = 7)
Randomization (1:1)
N = 82
Phase 2b
Primary Objective:
Assess early efficacy of PAN + AZA vs AZA alone
PAN + AZA (n = 40)
AZA (75 mg/m²) + PAN (RP2D)
AZA (n = 42)
AZA (75 mg/m²)

Figure 2.

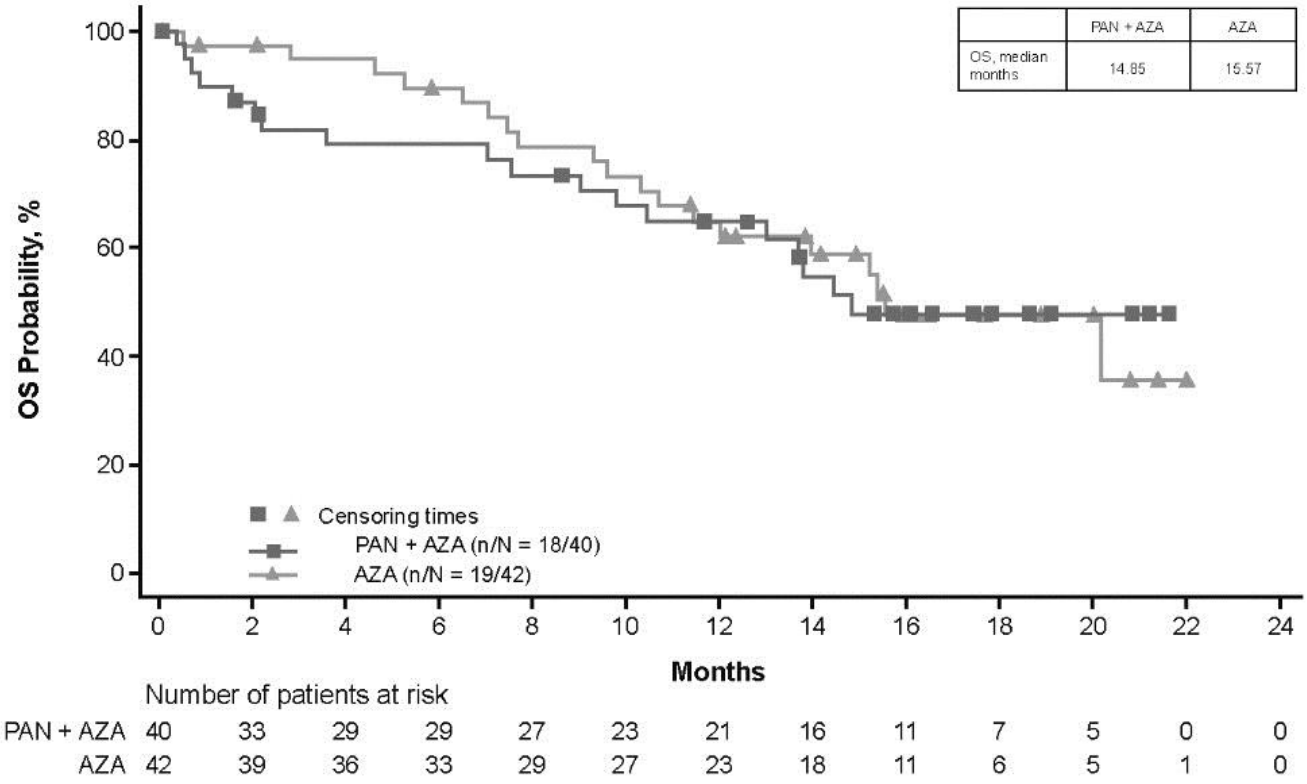
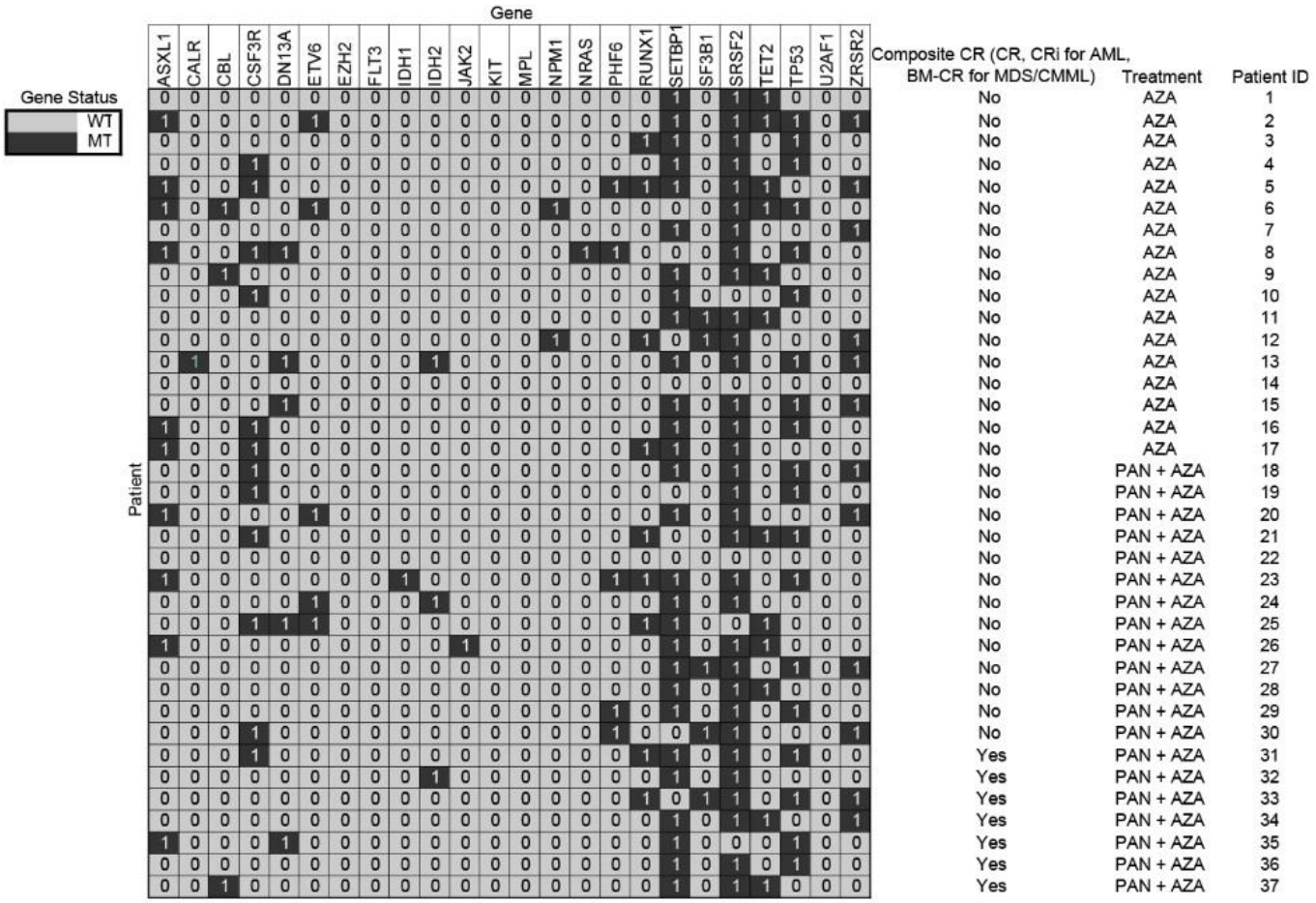

PAN + AZA
AZA
OS, median months
14.85
15.57
OS Probability, %
100
80
60
40
20
0
Censoring times
PAN + AZA (n/N = 18/40)
AZA (n/N = 19/42)
0
2
4
6
8
10
12
14
16
18
20
22
24
Months
Number of patients at risk
PAN + AZA 40 33 29 29 27 23 21 16 11 7 5 0 0
AZA 42 39 36 33 29 27 23 18 11 6 5 1 0

Figure 3.


Gene
Gene Status
WT
MT
Patient
ASXL1 CALR CBL CSF3R DN13A ETV6 EZH2 FLT3 IDH1 IDH2 JAK2 KIT MPL NPM1 NRAS PHF6 RUNX1 SETBP1 SF3B1 SRSF2 TET2 TP53 U2AF1 ZRSR2
Composite CR (CR, CRi for AML, BM-CR for MDS/CMML)
Treatment
Patient ID
No AZA 1
No AZA 2
No AZA 3
No AZA 4
No AZA 5
No AZA 6
No AZA 7
No AZA 8
No AZA 9
No AZA 10
No AZA 11
No AZA 12
No AZA 13
No AZA 14
No AZA 15
No AZA 16
No AZA 17
No PAN + AZA 18
No PAN + AZA 19
No PAN + AZA 20
No PAN + AZA 21
No PAN + AZA 22
No PAN + AZA 23
No PAN + AZA 24
No PAN + AZA 25
No PAN + AZA 26
No PAN + AZA 27
No PAN + AZA 28
No PAN + AZA 29
No PAN + AZA 30
Yes PAN + AZA 31
Yes PAN + AZA 32
Yes PAN + AZA 33
Yes PAN + AZA 34
Yes PAN + AZA 35
Yes PAN + AZA 36
Yes PAN + AZA 37

Supplementary Table 1. Genes Sequenced via Next-Generation Sequencing in the Phase 2b Portion

	Gene	Exons
RNA splicing	*SF3B1*	13-16
	SRSF2	1
	U2AF1	2, 6
	ZRSR2	2-5, 7-11
Epigenetic	*ASXL1*	12-13
	DNMT3A	7-22
	EZH2	1-19
	IDH1	2
	IDH2	4
	SETBP1	3
	TET2	1-9
Transcription factors	*ETV6*	1-8
	PHF6	1-9
	RUNX1	3-8
Activated signaling	*CBL*	7-9
	JAK2	10-12
	KIT	8-11, 13, 17-18
	MPL	10-11
	NRAS	1, 2
Other	*CALR*	9
	CSF3R	1-15
	FLT3	14, 20, no ITD
	NPM1	10-11
	TP53	1-10

Supplementary Table 2. Best Overall Response for Patients With MDS/CMML in the Phase 2b Portion

Best Response	PAN+AZA n = 31	AZA n = 29	All Patients n = 60
Clinical response (CR, BM-CR, PR), n (%) (95% CI)	13 (41.9) (24.5-60.9)	12 (41.4) (23.5-61.1)	25 (41.7) (29.1-55.1)
CR, n (%)	5 (16.1)	2 (6.9)	7 (11.9)
BM-CR, n (%)	4 (12.9)	1 (3.4)	5 (8.3)
PR, n (%)	0	2 (6.9)	2 (3.3)
SD, n (%)	5 (16.1)	5 (17.2)	10 (16.7)
Disease progression, n (%)	1 (3.2)	3 (10.3)	4 (6.7)
Unknown, n (%)	16 (51.6)	16 (55.2)	32 (53.3)
Relapse, n (%)	2 (6.5)	0	2 (3.3)
Relapse after CR, n (%)	1 (3.2)	0	1 (3.2)
Relapse after BM-CR,n (%)	1 (3.2)	0	1 (3.2)
Relapse after PR, n (%)	0	0	0

Abbreviations:AZA, azacitidine; BM-CR, bone marrow complete response; CR, complete response; PAN, panobinostat; PR, partial response; SD, stable disease.

Supplementary Table 3. Best Overall Response for Patients With AML in the Phase 2b Portion

Best Response	PAN+AZA n = 9	AZA n = 13	All Patients n = 22
Clinical response (CR, BM-CR, PR, HI), n (%) (95% CI)	2 (22.2) (2.8-60.0)	4 (30.8) (9.1-61.4)	6 (27.3) (10.7-50.2)
CR, n (%)	1 (11.1)	2 (15.4)	3 (13.6)
CRi, n (%)	1 (11.1)	1 (7.7)	2 (9.1)
PR, n (%)	0	1 (7.7)	1 (4.5)
Treatment failure, n (%)	4 (44.4)	6 (46.2)	10 (45.5)
Unknown, n (%)	3 (33.3)	3 (23.1)	6 (27.3)
Relapse, n (%)	0	5 (38.5)	5 (22.7)
Relapse after CR, n (%)	0	2 (15.4)	2 (9.1)
Relapse after BM-CR,n (%)	0	1 (7.7)	1 (4.5)
Relapse after PR, n (%)	0	1 (7.7)	1 (4.5)

Abbreviations: CRi,morphologic complete response with incomplete blood count; HI, hematologic improvement.