Planned Interim Analysis of a Phase 2 Study Evaluating the Combination of Pracinostat, a Histone Deacetylase Inhibitor, and Azacitidine in Patients with High/Very High-Risk Myelodysplastic Syndrome

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BACKGROUND

- Higher risk myelodysplastic syndrome (MDS) is a serious disease associated with poor survival, particularly in those patients with high/very high-risk disease by International Prognostic Scoring System- Revised (IPSS-R).
- Hypomethylating agents (HMAs) azacitidine and decitabine are the standard of care in patients with higher-risk MDS ineligible for stem cell transplantation.[1]
- Unfortunately, HMAs are only effective in 30-40% of patients, with the duration of response typically shorter than 1.5 years.[2] This has led to the evaluation of combination therapies to improve outcomes in higher risk MDS.
- Inhibition of both histone deacetylation (HDAC) and DNA hypermethylation has been shown to induce re-expression of silenced genes in myeloid malignancies in a synergistic fashion[3] and preclinical data suggest that the combination of hypomethylating agents like azacitidine (AZA) with HDAC inhibitors could be synergistic in vivo.[3,4]
- Studies have evaluated HMAs in combination with HDAC inhibitors but the results have been disappointing due to increased toxicity leading to early discontinuations.[5-7]
- Pracinostat, a potent oral Class I, II, IV HDAC inhibitor, has been studied in combination with standard dose AZA in a prior placebo-controlled Phase 2 study in 102 patients with HMA-naive IPSS intermediate-2/high risk MDS.[8]
- In the prior Phase 2 study, pracinostat was administered at 60 mg/day on 3 alternate days/week for 3 weeks/month, with step-down dose to 45 mg in case of poor tolerability in combination with AZA at 75 mg/m^2 x 7 days in a 28-day cycle. Toxicity, primarily cytopenias, nausea, vomiting and fatigue resulted in early discontinuations in the first 3 cycles in 26% of patients, potentially leading to diminished efficacy and no observed benefit of the pracinostat/AZA combination compared with AZA alone. In a post-hoc analysis, the subset of patients who received at least 4 cycles of pracinostat/AZA had a trend for better progression-free and overall survival compared to the control group suggesting the lack of efficacy in the overall population may have been due to early discontinuations and insufficient exposure to pracinostat/AZA.
- This follow-up study is evaluating a lower 45 mg dose of pracinostat (25% reduction) in combination with the standard dose of AZA with the goal of enhancing tolerability, decreasing early discontinuations, and improving outcomes.
  - 40 mg induced a 2-fold increase in histone 3 acetylation (acH3) in a Phase 1 study.
  - In prior MDS/AML studies ~50% of subjects achieved response and clinical benefit for more than a year with a step-down dose of 45 mg pracinostat.

METHODS

Objective

- The primary objectives of this study are to determine the safety, tolerability, and efficacy of pracinostat plus AZA in patients with high/very high risk MDS previously untreated with HMAs.
- This presentation reports the results of this ongoing study as of October 2018.

Study Design

- This is a multicenter, open-label, two-stage design, Phase 2 study being conducted at 24 sites.
- Up to 40 subjects were to enroll in Stage 1, treated with pracinostat at 45 mg, 3 days each week for 3 consecutive weeks, followed by 1 week of rest, along with AZA at the standard dose of 75 mg/m^2 for 7 days of each 28-day cycle. It was anticipated that enrolling ~40 subjects would result in at least 20 subjects followed for at least 3 cycles and informative to make a decision to expand to Stage 1b.
- Study drugs are to be administered until disease progression, intolerable toxicity, or referral for allogeneic stem cell transplantation (SCT), avoiding early discontinuation (<6 months) due to lack of response.
- As pre-defined thresholds were met for both early discontinuation rate and overall response rate, expansion of the open-label cohort in Stage 1b has occurred with ongoing recruitment towards a total of ~60 evaluable patients.

Key Inclusion Criteria

- Age ≥65 years with histologically or cytologically documented MDS according to WHO classification
- Classified as high- or very high-risk MDS according to the IPSS-R
- CMML-1 and CMML-2 subtypes were allowed
- Bone marrow biopsy and/or aspirate within 28 days prior to Day 1
- Eastern Cooperative Oncology Group (ECOG) performance score of 0–2
- Previously untreated with HMAs (prior therapy with transfusions, hematopoietic growth factors, or immunosuppressive therapy is allowed) and clinical indication for treatment with AZA

Key Exclusion Criteria

- Bone marrow blasts ≥20%, indicating a diagnosis of acute myeloid leukemia (AML)
- Received any investigational agent within 14 days or 5 half-lives prior to enrollment, hydroxyurea within 48 hours prior to first day of study treatment, or hematopoietic growth factors: erythropoietin, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), or thrombopoietin receptor agonists at least 7 days (14 days for Aranesp) prior to study enrollment
- Major surgery within 28 days prior to first study treatment
- Current unstable arrhythmia requiring treatment, history of symptomatic congestive heart failure (New York Heart Association [NYHA] Class III or IV), history of myocardial infarction within 6 months of enrollment, or current unstable angina
- Prior treatment for MDS with the HDAC inhibitor or investigational agent with significant action as an HDAC inhibitor

Assessments and Statistical Analysis

- For the pre-planned interim analysis, a pre-defined discontinuation rate due to adverse events (AEs) of ≤ 10% in the first 3 cycles (i.e., "early discontinuations") and an overall response rate of ≥ 20% were required to support expanded enrolment into Stage 1b, wherein approximately 20 additional patients will be treated for a total of 60 patients evaluable for response assessment.
  - A sample size of 60 patients was considered sufficient to detect a substantial effect on overall response rate compared to historical controls treated with AZA alone.
- Decision to expand to Stage 1b was based on review of safety by the Independent Data Monitoring Committee (IDMC) in conjunction with the study Sponsor.
- The primary efficacy endpoint is overall response rate (ORR) [defined as complete remission (CR), partial remission (PR) and marrow CR]. Response evaluation is performed after 2 and 6 cycles of therapy, and then every 6 months or as clinically indicated.
- Efficacy is being evaluated by Investigator assessments based on hematological and cytogenetic examination of peripheral blood and bone marrow aspirates and biopsy, as well as transfusions administered. Disease assessment is according to the IWG-R criteria.[9]
- Safety is being assessed primarily by AEs (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03), but also by laboratory tests, physical examination, vital signs, ECOG performance status, and 12-lead ECG.

RESULTS

Pre-Planned Interim Analysis

- The interim analysis for expansion was performed in May 2018; 40 patients had been enrolled and received ≥ 1 dose of study drug, of which 20 patients were deemed evaluable, having received ≥ 3 cycles of therapy or having discontinued study drug due to an adverse event prior to start of Cycle 4.
- 2/20 (10%) discontinued due to adverse events in the first 3 cycles, 1 after 1 cycle due neutropenic fever and the other after 2 cycles due to a fungal esophagitis and neutropenic fever.
- In 18 subjects evaluable for response assessment at the end of Cycle ≥ 2, the ORR was 28% (1 complete response, 4 partial responses).
- This early discontinuation rate of 10% met the preplanned interim analysis threshold for expansion and the IDMC authorized expansion to Stage 1b.

Baseline Characteristics

- Between June 2017 and October 2018, a total of 55 patients were enrolled at 17 US centers and received ≥ 1 dose of study treatment.
- The majority of patients were male (64%) with a median age of 68 years **(Table 1)**. The median time from diagnosis was 1 month and patients were generally split between high- and very high-risk MDS.

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Pracinostat + AZA N = 55
Sex	
Male	**35** (64%)
Female	**20** (36%)
Age (years)	
Median (range)	**68** (47-89)
No. (%) Age ≥ 75 years	**13** (24%)
MDS Subtype (WHO)	
MDS with excess blasts-2	**22** (40%)
MDS with excess blasts-1	**14** (25%)
MDS with multilineage dysplasia	**11** (22%)
CMML	**5** (9%)
MDS with ringed sideroblasts	**1** (2%)
MDS with del 5q	**1** (2%)
IPSS-R Risk Group (in MDS only)	**N = 50**
High-risk	**26** (52%)
Very high-risk	**23** (46%)
Not reported	**1** (2%)
Cytogenetic Risk Group	
Very good	**2** (4%)
Good	**20** (36%)
Intermediate	**5** (9%)
Poor	**8** (15%)
Very Poor	**18** (33%)
Not reported yet	**2** (4%)
Median Time (months) from Diagnosis (range)	**1** (0-17.9)

Patient Disposition

- As of October 25, 2018, 22 patients (40%) had discontinued study drugs **(Table 2)**.
- Five patients (9%) discontinued due to adverse events, of which 2 (4%) were considered early discontinuations (within the first 3 months/cycles).
- For the remaining 33 (60%) patients, the median duration on therapy is 4.7 months (range, 0.5-13 months).
- 14 patients (25%) had received > 6 cycles of therapy.

Table 2. Reason for Discontinuation (N = 22)

Reason	No. of Patients (%) N = 55	Week of Discontinuation
SCT	**8** (15%)	12, 16, 19, 25, 30, 32, 34, 39
Withdrawal of Consent	**5** (9%)	9, 16, 20, 21, 40
Adverse Event	**5** (9%)	0*, 7, 13, 15, 39
Progressive Disease	**3** (5%)	6, 8, 34
Physician Decision/Insurance	**1** (2%)	0*

* discontinued on Day 1 after 1 dose of study drug;
SCT: allogeneic stem cell transplantation

Safety

- The most common non-hematologic AEs were constipation (49%), nausea (47%), fatigue (35%) and decreased appetite (35%); the most common hematologic AEs were febrile neutropenia (40%) and anemia (35%) **(Table 3)**.

Table 3. Adverse Events in ≥20% of Patients (N = 55)

Adverse Event	Grade ≥3 n (%)	All Grades n (%)
Non-Hematologic		
Constipation	**0** (0)	**27** (49)
Nausea	**1** (2)	**26** (47)
Fatigue	**4** (7)	**19** (35)
Decreased appetite	**1** (2)	**19** (35)
Diarrhea	**1** (2)	**15** (27)
Edema peripheral	**0** (0)	**14** (26)
Hypoalbuminemia	**2** (4)	**13** (24)
Dyspnea	**2** (4)	**12** (22)
Hypokalemia	**1** (2)	**12** (22)
Vomiting	**2** (4)	**11** (20)
Dizziness	**0** (0)	**11** (20)
Hematologic		
Febrile neutropenia	**21** (38)	**22** (40)
Anemia	**18** (33)	**19** (35)
Neutropenia	**18** (33)	**18** (33)
Thrombocytopenia	**14** (26)	**15** (27)

- The incidences of key adverse events that led to early discontinuations in the prior study were lower in the current study for most of the AEs **(Table 4)**.

Table 4. Key Adverse Events in Current Study Compared to Prior Study[8]

	Grade ≥3 (% Patients)		All Grades (% Patients)	
Adverse Event	Current Study N = 55	Prior Study N = 51	Current Study N = 55	Prior Study N = 51
Non-Hematologic				
Constipation	**0**	**2**	**49**	**53**
Nausea	**2**	**4**	**47**	**69**
Fatigue	**7**	**24**	**35**	**55**
Vomiting	**4**	**4**	**20**	**47**
Hematologic				
Febrile neutropenia	**38**	**33**	**40**	**33**
Anemia	**33**	**20**	**35**	**31**
Neutropenia	**33**	**45**	**33**	**45**
Thrombocytopenia	**26**	**47**	**27**	**49**

Deaths

- Nine patients (16%) have died, 5 due to PD and 4 due to AEs; of these 5 patients (9%) died while on study or within 28 days of discontinuing study drug (2 due to PD, 3 due to AEs).
- Two patients died in the first 2 months on study, for a 60-day all-cause mortality of 3.6%.

Efficacy

- As of October 25, 2018, in the 45 patients deemed evaluable for response, the ORR was 29% **(Table 5)**.

Table 5. Best Disease Response

Endpoint	Patients Evaluable for Efficacy from the Stage 1 Interim Analysis Subset* (N = 19)	All Patients Evaluable for Response at Cycle 2 and/or at Later Cycles* (N = 45)	All Patients Who Reached Cycle 6 or Discontinued Before Cycle 6** (N = 33)
Complete response (CR)	**7** (37%)	**13** (29%)	**12** (36%)
Partial Response (PR)	**0** (0%)	**0** (0%)	**0** (0%)
Overall Response Rate (ORR)	**7** (37%)	**13** (29%)	**12** (36%)
Marrow CR + Hematologic Improvement (HI)	**2** (10%)	**5** (11%)	**4** (12%)
Marrow CR	**2** (10%)	**9** (20%)	**6** (18%)
Stable Disease + HI	**3** (16%)	**4** (9%)	**4** (12%)
Stable Disease	**3** (16%)	**11** (24%)	**4** (12%)
Progressive Disease (PD)	**2** (10%)	**3** (7%)	**3** (9%)

*At least one disease assessment after baseline; ** Excludes ongoing patients who have not reached Cycle 6

CONCLUSIONS

- This study evaluating the efficacy and safety of pracinostat + AZA in patients with high-/very high-risk MDS showed that the lower dose of 45 mg pracinostat is better tolerated than the 60 mg dose evaluated in the prior study[8].
- The incidences of adverse events that led to early discontinuations in the prior study were lower for non-hematological events and at least comparable for hematological events in the current study; it is noteworthy that patients in this study were higher-risk MDS than the prior study.
- A discontinuation rate due to adverse events in the first 3 months of 4% is substantially lower than the rate of 26% reported in the prior study and to that reported in prior studies with AZA alone.
- The CR rate of 29% is encouraging; further follow-up is needed to evaluate the effect on survival.
- While enrolment in this study is continuing, the initial results are promising in showing that this lower dose pracinostat/AZA combination enhances tolerability, decreases early discontinuations, and improves clinical outcomes compared with the prior study in MDS.

REFERENCES: 1. NCCN Guidelines Myelodysplastic Syndromes. Version 2.2019. **2.** Fenaux P, et al. Lancet Oncol 2009;10(3):223-232. **3.** Cameron EE, et al. Nat Genet 1999;21:103-107. **4.** Schneider-Stock R, Ocker M. IDrugs 2007;10:557-561. **5.** Sekeres, JCO 2017;35(24):2745-2753. **6.** Prebet, JCO 2011;29(24):3322-3327. **7.** Garcia-Manero, Lancet 2016;17(4):496-508. **8.** Garcia-Manero G, et al. Cancer 2017. **9.** Cheson Blood 2006;108(2):419-425.

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