Very High Rates of Clinical and Cytogenetic Response with the Combination of the Histone Deacetylase Inhibitor Pracinostat (SB939) and 5-Azacitidine in High-Risk Myelodysplastic Syndrome

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Abstract

Background — Pracinostat (SB939) is a dialkyl benzimidazole competitive inhibitor of histone deacetylase (HDACi) that has >1000-fold selectivity for HDAC Class 1 and 2 *versus* Class 3. Antitumor activity has been demonstrated in xenograft models of AML (MV4-11). We conducted a phase I study with pracinostat in patients with advanced myelodysplastic syndrome (MDS; n=11), acute myeloid leukemia (AML; n=12), and lymphoma (n=1). Pracinostat demonstrated excellent PK properties and target inhibition and was generally well tolerated. The MTD was not reached. Activity was documented in 9 patients (1 CR, 1 PR, 7 SD), which encouraged further exploration of pracinostat-based combinations. The recommended phase II dose was 100 mg daily. The combination of 5-azacitidine and HDACi is known to be safe and active in MDS and AML.

Methods — This is a pilot phase II study conducted as an extension study in the context of a phase I trial of pracinostat in hematological malignancies to determine the efficacy and safety of the combination of pracinostat (60 mg orally every other day 3 times a week for 3 consecutive weeks) and 5-azacitidine (75 mg/m^2 IV daily x 5 every 3 to 6 weeks) given in 4-week cycles to patients with intermediate-2 or high risk MDS.

Results — Nine patients (6 women) were accrued between May 2011 and September 2011. Median age was 64 years (range, 22-73), WBC 2.4x10^9/dL (0.7-9.3), Hg 10g/dL (8.2-11), platelets 31x10^9/dL (14-269), and bone marrow blasts 7% (0%-18%). Seven (78%) patients had therapy related MDS with history of prior chemotherapy/radiotherapy exposure (3 breast cancer, 2 non-Hodgkin's lymphoma, 1 breast and ovarian cancer, and 1 melanoma). Three patients had failed prior therapy: decitabine and haploidentical stem cell transplantation (SCT; n=1), lenalidomide (n=1), and decitabine and TXA-127 (n=1). All patients carried cytogenetic abnormalities: complex (n=4, 3 including -7 and 1 with -5), -7 (n=3, one of them with +8), t(6;9) (n=1), and t(14;16) and del(20) (n=1). Two patients with -7 also carried gene mutations: 1 in CEBPa and 1 IDH2^{R140Q}. Patients received a median of 4 cycles. All 9 patients are evaluable. The overall response rate (ORR; defined as CR+CRi+PR) is 8/9 (89%) and the CR+CRi rate is 7/9 (78%). Five (56%) patients achieved a complete cytogenetic response, including the patient carrying IDH2R140Q, in whom such mutation became undetectable. Eight-week mortality was 0%. Only 1 (11%) patient has died, unrelated to study drug (after allogeneic-SCT). The median duration of response was 45 days (0-229). Reasons for discontinuation were: transition to allogeneic-SCT (n=5), no pracinostat availability by sponsor (n=2), no response (n=1), and progression to AML (n=1). The combination was well tolerated. All toxicities were grade 1 or 2. The most frequent toxicities were fatigue and nausea (56% each).

Conclusion — The combination of pracinostat and 5-azacitidine was very well tolerated in patients with MDS. The preliminary ORR of 89% is very encouraging, considering that most patients in this study had high-risk cytogenetics and/or had treatment related MDS, both subsets of MDS with very poor prognosis.

Background – MDS Therapy

- Loss of gene function in MDS is frequently caused by epigenetic transcriptional silencing through methylation of the cytosine residues within CpG dinucleotides and/or posttranslational deacetylation of histones
- Reversing epigenetic changes with DNA hypomethylating agents such as 5-azacitidine (AZA) has changed the therapeutic paradigm in MDS.
- Combinations of hypomehtylating agents and histone deacetylase inhibitors (HDACi) may improve the results observed with single agent hypomethylating therapy.

Background – Pracinostat (SB939)

- Pracinostat (SB939) is a dialkyl benzimidazole competitive HDACi with >1000-fold selectivity for HDAC Class 1 and 2 *versus* Class 3. Antitumor activity has been demonstrated in xenograft models of AML (MV4-11).
- We conducted a phase I study of pracinostat in patients with advanced MDS (n=11), acute myeloid leukemia (AML; n=12), and lymphoma (n=1).
- Pracinostat demonstrated excellent PK properties and target inhibition and was generally well tolerated.
- The MTD was not reached and activity was observed in 9 patients (1 CR, 1 PR, 7 SD), which encouraged further exploration of pracinostat-based combinations.
- The recommended phase II dose was 100 mg daily.
- The combination of AZA and HDACi is known to be safe and active in MDS and AML.

Objectives

- Given that the combination of AZA and HDACi has been shown to be safe and active in MDS and AML, we designed a study to assess the efficacy and tolerability of the combination of AZA and pracinostat in patients with high-risk MDS.

Patients and Methods

- This is a pilot phase II study conducted as an extension study in the context of a phase I trial of pracinostat in hematological malignancies
- Patients included in this pilot study had a diagnosis of intermediate-2 or high-risk MDS according to IPSS
- Combination therapy consisted of:
  - pracinostat (60 mg orally every other day 3 times a week for 3 consecutive weeks)
  - AZA (75 mg/m^2 IV daily x 5 every 3 to 6 weeks) given in 4-week cycles

Patient Characteristics

	Median (range)	No. (%)
Age (y)	64 (19-73)	
Male		3 (33)
WBC (x10^9/L)	2.4 (0.7-9.3)	
Hemoglobin (g/dL)	10.1 (8.2-11.3)	
Platelets (x10^9/L)	31 (14-269)	
Bone marrow blasts (%)	7 (0-18)	5 (10)
Therapy-related MDS		7 (78)
breast cancer		3 (33)
breast + ovarian cancer		1 (11)
non-Hodgkin´s lymphoma		2 (22)
Melanoma		1 (11)
Prior MDS therapy		3 (33)
decitabine, haploidentical SCT		1 (11)
lenalidomide		1 (11)
decitabine, TXA-127		1 (11)
Abnormal karyotype		9 (100)
Complex		4 (44)
-7		3 (33)
t(6;9)		1(11)
t(14;16) + del20		1 (11)
Patients with high-risk karyotype		7 (77)
Complex		4 (44)
-5 and/or -7		3 (33)
Gene mutations		2 (22)
IDH2R140Q		1 (11)
CEBPA		1 (11)

Results

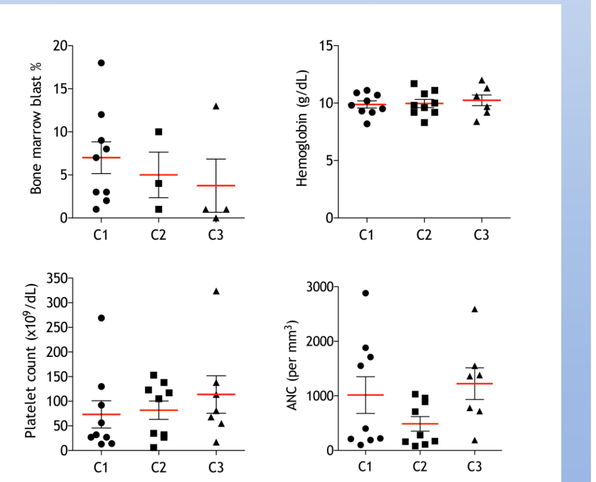
- Patients received a median of 4 cycles.
- All 9 patients were evaluable for efficacy and toxicity analyses.
- The overall response rate (ORR; defined as CR + CRi + PR) was 8/9 (89%).
- Seven of the 9 patients (78%) achieved either CR or CRi.
- Five (56%) patients achieved a complete cytogenetic response, including the patient who also carried an IDH2^{R140Q} mutation, in whom such mutation became undetectable.
- The 8-week mortality was 0%.
- Only 1 (11%) patient has died, unrelated to any of the study drugs, after allogeneic-SCT.
- The median duration of response was 45 days (range, 0-229).

Toxicity

	Overall, N (%)	Grade 3-4, N(%)
Nausea	9 (100)	0
Fatigue	7 (78)	0
Elevated BUN/creatinine	5 (56)	0
Vomiting	4 (44)	0
Hyperbilirubinemia	4 (44)	0
Constipation	4 (44)	0
Periodontitis	3 (33)	0
Neutropenic fever	2 (22)	2 (22)
Rash	2 (22)	0
Hypomagnesemia	2 (22)	0
Thrombocytopenia	2 (22)	2 (22)
Neutropenic fever	2 (22)	1 (11)

Only toxicities reported in at least one patient are shown

Peripheral Blood Count Dynamics



Only counts during the first 3 cycles ("C") of therapy are shown

Conclusions

- The combination of pracinostat and 5-azacitidine was very well tolerated in patients with MDS.
- The preliminary ORR of 89% is very encouraging, considering that most patients in this study had high-risk cytogenetics and/or had treatment related MDS, both of them subsets of MDS with very poor prognosis.

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Disclosures

GGM and AQC received research support from SBIO