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


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Abstract

Background - Pracinostat (SB939) is a dialkyl benzamidinazole 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 syndromes (MDS), acute myeloid leukemia (AML), and lymphoma (n=1). Pracinostat demonstrated excellent PK properties and target inhibition was generally well tolerated. The MTD was not reached. Activity (n=1), and progression 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-azadcidine 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 safety of the combination of pracinostat (60 mg orally every other day 3 times a week for 3 consecutive weeks) and 5-azadcidine (75 mg/m² 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 2.4x10³/μL (0.7-9.3), Hg 10.1g/dL (8.2-11.3), platelets 31x10³/μL (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, 10q(9)/n=1, and 14q(t14;16) and del(20). Two patients with -7 also carried gene mutations: 1 in CEBPB and 1 IDH2R1408. Patients received a median of 4 cycles. All 9 patients were evaluable. The overall response rate (ORR; defined as CR+PR+BR) is 89% (9/10) and the CR+PR rate is 79% (7/9). Five (56%) patients achieved a complete cytogenetic response, including the patient carrying IDH2R1408, 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 (0.2-229). Reasons for discontinuation were: transition to allo-SCT (n=3), 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-azadcidine was generally well tolerated in patients with MDS. The preliminary ORR of 89% was 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.

Peripheral Blood Count Dynamics

Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Overall, N (%)</th>
<th>Grade 3-4, N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>9 (100)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (78)</td>
<td></td>
</tr>
<tr>
<td>Elevated BUN/creatinine</td>
<td>5 (56)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (22)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (22)</td>
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</tr>
<tr>
<td>Hypomagnesemia</td>
<td>2 (22)</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>2 (22)</td>
<td>2 (22)</td>
</tr>
</tbody>
</table>

Peripheral Blood Count Dynamics

Only toxicities reported in at least one patient are shown.

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 + PR + BR) was 89% (9/10).
- Seven of the 9 patients (78%) achieved either CR or PR.
- Five (56%) patients achieved a complete cytogenetic response, including the patient who also carried an IDH2R1408 mutation, in whom such mutation became undetectable.
- The 8-week mortality was 0%.
- Only 1 (11%) patient had died, unrelated to any of the study drugs, after allogeneic-SCT.
- The median duration of response was 45 days (range, 0-229).

Conclusions

- The combination of pracinostat and 5-azadcidine 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