Results of the Initial Treatment Phase of a Study of Three Alternative Dosing Schedules of Azacitidine (Vidaza®) in Patients with Myelodysplastic Syndromes (MDS). Session Type: Oral Session

Roger M. Lyons, Thomas Cosgriff, Sanjiv Modi, Heidi McIntyre, Indra Fernando, Jay Backstrom, C.L. Beach Cancer Care Centers of South Texas, San Antonio, TX, USA; Hematology and Oncology Specialists, New Orleans, LA, USA; Joliet Oncology-Hematology Associates, Ltd, Joliet, IL, USA; Pharmion Corporation, Overland Park, KS, USA

Background: Azacitidine (Vidaza®) is an effective and safe treatment (Tx) for patients (pts) with MDS (JCO 2002;20:2429) at a dosing schedule of 75 mg/m²/day SC for 7 days every 4 weeks. A dosing schedule eliminating the need for weekend administration would be more convenient to pts and clinicians. Reported here are results of the recently completed initial Tx phase (6 cycles of randomized Tx) of an ongoing study evaluating 3 alternative azacitidine dosing schedules. Methods: In this phase II multicenter, open-label trial, MDS pts were randomized to 1 of 3 regimens administered every 4 weeks for 6 cycles: AZA 5-2-2 (75 mg/m²/day x 5 days, followed by 2 days no Tx, followed by 75 mg/m²/day x 2 days); AZA 5-2-5 (50 mg/m²/day x 5 days, followed by 2 days no Tx, followed by 50 mg/m²/day x 5 days); or AZA 5 (75 mg/m²/day x 5 days). Major and minor hematologic improvements (HI) were assessed by International Working Group (IWG) criteria (Blood 2000;96:3671) and pts with ≥56 Tx days were IWG evaluable. To determine whether therapeutic response is maintained after 6 cycles, a 12-month maintenance phase using the AZA-5 regimen administered every 4 or 6 weeks was added, and pts with at least stable disease were eligible to participate in that phase of the study. Results: A total of 151 pts were randomized to Tx with AZA 5-2-2 (n=50), AZA 5-2-5 (n=51), or AZA 5 (n=50). Most pts are FAB classification RA/RARS (57%) or RAEB (30%). Of the 139 pts (92%) who received ≥56 days of Tx and are IWG evaluable, 74 pts (49%) completed ≥6 Tx cycles. The median number of Tx cycles across all Tx arms was 6. Of IWG-evaluable pts, 71 (51%) experienced HI (Table). The proportions of red blood cell (RBC) transfusion-dependent pts who achieved transfusion independence were AZA 5-2-2: 55% (12/22), AZA 5-2-5: 60% (12/20), and AZA-5: 67% (16/24). In FAB low-risk (RA/RARS) transfusion-dependent pts at baseline, RBC transfusion independence was reached by 60% (9/15), 56% (5/9), and 61% (11/18), respectively. No Tx-related mortality has been reported. Most grades 3 and 4 Tx-related AEs were hematological (AZA 5-2-2: 44%, AZA 5-2-5: 33%, AZA 5: 18%). Conclusions: Independent of the alternative dosing regimen, the results of the initial 6-cycle Tx phase demonstrate a consistent response for HI, RBC transfusion independence, and safety profile across a broad range of MDS pts, including FAB low-risk pts. These results appear similar to those with the approved FDA regimen and further support the benefit of azacitidine in pts who are transfusion-dependent. Eligible pts continue to receive Tx during the ongoing 12-month maintenance phase of the study.

Major Hematologic Improvement in IWG Evaluable Pts (N=139)

<table>
<thead>
<tr>
<th>Major HI</th>
<th>AZA 5-2-2 (N=46)</th>
<th>AZA 5-2-5 (N=44)</th>
<th>AZA 5 (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) (95% CI)</td>
<td>n (%) (95% CI)</td>
<td>n (%) (95% CI)</td>
</tr>
<tr>
<td>Erythroid</td>
<td>15 (33) (20, 48)</td>
<td>17 (39) (24, 55)</td>
<td>19 (39) (25, 54)</td>
</tr>
<tr>
<td>Platelet</td>
<td>10 (22) (11, 36)</td>
<td>8 (18) (8, 33)</td>
<td>9 (18) (9, 32)</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>3 (7) (29, 100)</td>
<td>4 (9) (40, 100)</td>
<td>4 (8) (40, 100)</td>
</tr>
<tr>
<td>Any HI*</td>
<td>20 (44) (29, 59)</td>
<td>23 (52) (37, 68)</td>
<td>28 (57) (42, 71)</td>
</tr>
</tbody>
</table>

*Includes major and minor HI; pts counted only once for best response in an improvement category.
Abstract #819 appears in Blood, Volume 110, issue 11, November 16, 2007

Keywords: Hypomethylation|Regimen|Clinical Trial

Tuesday, December 11, 2007 8:00 AM

Session Info: Simultaneous Session: Myelodysplastic Syndromes: Advances in Therapeutic Options (7:30 a.m.-9:00 a.m.)
Results of the Initial Treatment Phase of a Study of Three Alternative Dosing Schedules of Azacitidine in Patients With Myelodysplastic Syndromes

**ABSTRACT 819**

R. M. Lyons,1 T. Cosgrove,2 S. Modi,3 H. McIntyre,4 J. Fernandez,5 J. Backstrom,6 and L. Beach7

1-Cancer Care Centers of South Texas, San Antonio, TX; 2, 3, Hematology and Oncology Specialty, New Orleans, LA; 4, Joint-Order Hematology-Oncology Associates, Ltd.; 5, 6, Scottish Physicians Cooperative, Overland Park, KS

**Introduction**

- Although the efficacy and safety of the currently approved azacitidine (AZA) 75 mg/m²/day for 7 days every 4 weeks has been established, alternative dosing regimens have been explored as a way to achieve higher response rates and improve the safety profile of AZA therapy.

**Methods**

- **Study Design**
  - Multicenter, randomized, double-blind, phase II trial.
  - Patients were randomized 1:1:1 to receive: AZA 5 mg/m²/day for 5 days, AZA 5 mg/m²/day for 2 days, or AZA 5 mg/m²/day for 1 day every 4 weeks (AZA 5-2-5).
  - Treatment continued for 3 cycles or for 36 cycles in patients who achieved transfusion independence.

- **Study End Points**
  - Conventional end points included overall response rate (ORR), overall hematologic improvement (HI), transfusion independence (TI), and duration of response (DR).

**Objectives**

- To evaluate the safety and efficacy of AZA 5 mg/m²/day for 1, 2, or 5 days every 4 weeks in patients with lower risk and intermediate 1 MDS.

**Results**

- **Patient Demographics and Drug Exposure**
  - Of the 151 patients enrolled, 149 were evaluable (50% AZA 5-2-5, 37% AZA 5-2-2, and 13% AZA 5-2-1). The median age was 73 (37-88) years, and 73% were male.

- **Hematologic Improvement**
  - AZA 5-2-5 achieved the highest overall response rate (ORR) and overall hematologic improvement rate (HI), with 43% and 67% of patients achieving an ORR and HI, respectively.

- **Transfusion Independence**
  - Patients in the AZA 5-2-5 arm achieved transfusion independence at a higher rate than those in the other arms (95% CI 60.6%-99.9%).

**Discussion**

- In the majority of patients, hematologic improvement in individual cell lines was observed in both MDS and peripheral blood stem cells.

**Conclusions**

- In conclusion, with similar efficacy and comparable adverse events, the AZA 5-2-5 regimen demonstrated improved transfusion independence, consistent overall and response rates, and higher hematologic improvement rates in this initial treatment phase, while allowing for the need of flexible dosing.

**References**

