Voreloxin Single-Agent Treatment of Older Patients (≥ 60 Years) With Previously Untreated Acute Myeloid Leukemia: Results From a Phase 2 Study With 3 Schedules

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Background: Voreloxin is a first-in-class anticancer quinolone derivative that intercalates DNA and inhibits topoisomerase II, inducing apoptosis. REVEAL-1, a phase 2 dose regimen optimization study of 3 schedules of single-agent voreloxin, was conducted in patients age 60 to 69 years with newly diagnosed acute myeloid leukemia (AML) and ≥ 1 additional adverse risk factor age (≥ 70), secondary AML, intermediate or unfavorable cytogenetics, or PS 2. These patients were thought to be unlikely to benefit from standard induction therapy. However, recent publications (Lowenberg 2009, Jaszczuk 2009) and NCCN 2010 guidelines indicate that many patients ≥ age 60 are eligible for conventional therapies.

Methods: Three voreloxin schedules were studied: A 72 mg/m2 on d1, 4, N = 29 or B 72 mg/m2 on d1, 4, 8, N = 29 or C 72 mg/m2 on d1, 4, N = 20. Eligibility newly diagnosed AML (de novo or secondary), patients age ≥ 60 with ≥ 1 additional adverse risk factor. Patients were allowed up to 2 cycles of induction and up to 2 additional cycles for consolidation (4 cycles total). Plasma and urine PK was evaluated in a 4-patient pilot cycle 1. Results: Schedule A was established in a phase 1 study in relapsed/refractory leukemia patients (Proc ASH 2007), and showed good activity but was too well-tolerated in this older, newly diagnosed population. Across all cohorts, most patients were male (66%) with a median age of 70 years (70% ≥ 70%, 70% had ECOG PS 0-1, and 30% had AML, from AHS as M5). Most patients had intermediate (8% or unfavorable) cytogenetics (25% had 2 or more risk factors. Schedule was optimized in successive cycles, after real-time review, to improve tolerability and maintain efficacy after review of schedule A data indicated good activity but excessive toxicity (Proc ASH 2009). The 4-dose schedule B (61%) was well-tolerated with improved tolerability, with cohort CT2 demonstrating the best overall outcome with 36% ORR, ANC recovery at 30 days, median OS 1.4 years, 1 year survival of 38% and 30% and 60-day all-cause mortality of 7% and 17%, respectively. Overall incidence of adverse events (AE) and serious adverse events (SAE) of infections and mucositis was reduced in B and C72. Voreloxin PK was similar in PK in the phase 1 study and in an ongoing phase 2 study in combination with cytarabine, and voreloxin clearance is nominal with <5% of total dose recovered in urine (Proc ASH 2009). Conclusions: In REVEAL-1, voreloxin demonstrated clinical activity in older patients with AML, and multi-risk factors. CT2, d1, 4 is appropriate for further development based on ORR (36%), median OS of 7.7 months, 30- and 60-day all-cause mortality (7% and 17%, respectively) and an improved safety profile with lower rates of AE and SAE of infection and mucositis than for A. Further studies are planned for voreloxin administered on a day 1 and 4 schedule as a single agent as well as in combination with cytarabine and other agents. A multinational, randomized, double-blind, placebo-controlled, phase 3 study of voreloxin in placebo in combination with cytarabine in relapsed or refractory AML is planned.

STUDY DESIGN

Population

Previously untreated patients with AML; ≥ 60 years or with one or more risk factors:

- Age ≥ 70 years
- AHD (≥ 1 allowed)
- ECOG PS 2
- Intermediate or unfavorable cytogenetics

Design

Single arm, sequential groups

Endpoints

- Overall remission rate (ORR) per NCCN criteria
- Safety, early mortality, PK, toxicity/freedom survival

DOSE AND SCHEDULE OPTIMIZATION

Schedule and Dose Regimen

<table>
<thead>
<tr>
<th>Schedule and Dose Regimen</th>
<th>A72</th>
<th>B72</th>
<th>C72</th>
<th>C90</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule and Dose mg/m2</td>
<td>d1, 15</td>
<td>d1, 8</td>
<td>d1, 4</td>
<td>d1, 4</td>
<td>All</td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>30</td>
<td>32</td>
<td>22</td>
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<tr>
<td>Male</td>
<td>86%</td>
<td>87%</td>
<td>89%</td>
<td>82%</td>
<td>65%</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>(61-84)</td>
<td>(64-87)</td>
<td>(61-84)</td>
<td>(64-87)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS 0-1</td>
<td>72%</td>
<td>73%</td>
<td>76%</td>
<td>81%</td>
<td>78%</td>
</tr>
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<td>76%</td>
<td>81%</td>
<td>78%</td>
</tr>
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<td>72%</td>
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<td>81%</td>
<td>78%</td>
</tr>
</tbody>
</table>

Voreloxin: An Anticancer Quinolone Derivative (AQD) (NCCN 2010)

- Novel, stable scaffold offers advantages over anthracyclines
- Interactions DNA and inhibits topoisomerase II
- Enables common drug resistance mechanisms
- Not a P-glycoprotein substrate
- Activity unaffected by p53, p63 or p73 status

- Unlike anthracyclines, does not produce in vivo substantial reactive oxygen species implicated in cardiotoxicity

ANATOMIC-CYTOGENETIC

Cytogenetic

NCCN 2018

Interradial

52% 37% 45% 90% 46%

Unfavorable

41% 46% 48% 30% 42%

Not available

7% 11% 9% 13% 8%

Risk Factors

1% 1% 12% 21% 16%

2.2 98% 88% 16% 85% 82%