**Clinical Evidence of Mechanism-Based Pharmacodynamic Activity in Voreloxin-Treated AML Patients**

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**ABSTRACT**

Voreloxin is a first-in-class anticancer quinolone derivative that intercalates DNA and poisons topoisomerase-I (Stockwell et al. et al. AACR 2003). This leads to replication-dependent, site-selective DNA double-strand breaks (DSB) resulting in G2 checkpoint arrest and cell death. A consequence of this DNA damage is G2 arrest and cell death by apoptosis. Voreloxin is under clinical investigation in acute myeloid leukemia (AML) and ovarian cancer. Clinical responses have been observed in these indications (Lunati et al. ASCO 2009; Ravandi et al. ASCO 2009; Hine et al. ASCO 2009; as well as in NSCLC and SCLC (Burns et al. ECCO 2007). The current analysis was performed in support of the ongoing phase 1b/2 study clinical study (SPO-0012) of voreloxin in combination with cytarabine in relapsed or refractory AML. The purposes were to (1) characterize voreloxin-induced biomarkers of mechanism-based pharmacodynamic (PD) activity in cell line and peripheral blood mononuclear cells (PBMC) from AML patients; (2) differentially profile the DDR response to voreloxin before and following the combination treatment with voreloxin and cytarabine in SPO-0012; to evaluate PD markers of cellular response; (3) investigate potential correlations between cellular PD markers of DNA damage and clinical outcome.

Based on our understanding of voreloxin’s mechanism of action, pharmacodynamic (PD) markers of 5 phase delay, G2 arrest and DNA damage following treatment with voreloxin were profiled in cell lines and then evaluated in AML PBMC. These included markers of stalled replication fork (pRPA32), and pDNA-PKcs(S2056) and pCHK2 (T68). The PD response was observed in Schedule A patients who received cytarabine, but these occurred later than with voreloxin treatment, which was characterized in these in vitro model systems. Cytarabine is a mainstay of treatment in AML, administered for 7 days per treatment cycle in combination with doxorubicin on days 1-3 (the “7+3” treatment schedule). Cytarabine is incorporated into DNA and causes inhibition of DNA polymerase resulting in decreased DNA synthesis and repair. DNA damage responses were observed with cytarabine, but these occurred later than with voreloxin treatment.

Voreloxin induction of pDNA-PKcs and pCHK2 were chosen for PD assessments in the ongoing phase 1b/2 study of voreloxin in combination with cytarabine in relapsed or refractory AML. PBMC were purified from blood samples collected from 10 patients immediately pre-treatment and post-treatment. Upregulation of pDNA-PKcs and pCHK2 was detected within 2 hours post dose, providing evidence of mechanism-based PD response to voreloxin. Concurrent imaging of FACS-propidium iodide and flow cytometry was used to preclude correlation of PD response with clinical outcome.

**VORELOXIN INDUCES DOSE- AND TIME-DEPENDENT MECHANISM-BASED PHARMACODYNAMIC MARKERS OF RESPONSE IN PRIMARY AML BLASTS**

The mechanism-based pharmacodynamic response to voreloxin is differentiable from that to cytarabine (Ara-C).

**VORELOXIN IS AN ANTICANCER QUINOLONE DERIVATIVE (AQD)**

Voreloxin is structurally unrelated to the anthracyclines, but has a similar mechanism of action:

- Voreloxin is a ribonucleotide analog, closely related to the anthracyclines, but has a different mechanism of action.
- Voreloxin intercalates DNA and poisons topoisomerase-I, causing site-selective DNA damage and apoptosis.
- Site-selective DNA damage is analogous to the quinolones in bacterial DNA.
- Voreloxin-induced activity is dose-dependent.
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- Voreloxin is active against anthracycline-resistant cells.
- Low potential for cardiomyopathy is due to a more chemically stable structure and minimal production of reactive oxygen species (ROS).
- Low risk of CYP450-mediated drug-drug interaction.

**VORELOXIN-INDUCED PHARMACODYNAMIC MARKERS ARE DETECTABLE IN PRIMARY AML BLASTS**

The in vivo pharmacodynamic response of voreloxin is differentiable from that to cytarabine (Ara-C).

**SUMMARY AND CONCLUSIONS**

- Voreloxin is a first-in-class anticancer quinolone derivative with Phase 2 clinical proof-of-concept in AML and ovarian cancer.
- Data reported here demonstrate mechanism-based pharmacodynamic activity of voreloxin in patients from the ongoing clinical trial of voreloxin in combination with cytarabine in relapsed/refractory AML.
- The DNA damage response to voreloxin is differentiable from that to cytarabine.
- The clinical development updates will be presented at the 2009 Annual Meeting of the American Society of Hematology (ASH).

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