Voreloxin is a first-in-class quinolone derivative that intercalates DNA and poisons topoisomerase II (Stockey et al. and Lerner et al., AACR 2003). This leads to replication-dependent, site-selective DNA damage, and induces cell cycle arrest and apoptosis (Stockley et al., AACR 2003; Bickert et al., AACR 2005; Stockley et al., AACR 2007). An advantage of the DNA intercalation mechanism is that it confers a broad therapeutic index in HL-60 acute promyelocytic leukemia (AML) and ovarian cancer. Clinical responses have been observed in these indications (Lynch et al., ASCO 2000; Bickert et al., ASCO 2005; Hime et al. ASCO 2003), as well as in HLBCC and EOCO (Barka et al. EOCO 2007).

The current analysis was performed in support of a Phase I/II clinical study (NCT0012102) of voreloxin in combination with cytarabine in relapsed or refractory AML, and to investigate the feasibility for combining voreloxin with other agents. Voreloxin activity combined with itself was used as control.

**METHOD**

Combination index (CI) was established using combined serial dilution of both compounds, starting at either 10x (High) or 1x (Low) IC50 dose titration vs combination IC50 for each agent. Combination index (CI) was calculated using the following equation:

\[
CI = \frac{IC_{50a} \times IC_{50b}}{IC_{50a} + IC_{50b}}
\]

**RESULTS AND DATA ANALYSIS**

Percent viability of cells treated with voreloxin alone and voreloxin combined with cytarabine was evaluated in 3 acute leukemic cell lines (HL-60 acute promyelocytic analogs), and clofarabine analog) was also studied in the HL-60 APL cell line. Cytotoxicity was assessed by proliferation inhibition.

**COMBINATION INDEX (CI) ANALYSIS**

Each data point represents an independent experiment.

**SUMMARY AND CONCLUSIONS**

- Voreloxin is a first-in-class anticancer quinolone derivative that intercalates DNA and poisons topoisomerase II, causing site-selective DNA damage and apoptosis.
- Site selective DNA damage is analogous to the quinolones in bacterial DNA.
- Broad therapeutic index.
- Voreloxin activity in acute leukemia and colorectal cancer.
- Voreloxin has a similar mechanism of action to the anthracyclines, but has a similar mechanism of action.
- These data support the ongoing phase 1/2 clinical study of voreloxin in combination with cytarabine in relapsed/refractory AML.
- Clinical development of voreloxin continues with ongoing studies in AML and platinum-resistant ovarian cancer.

**ADJACENCY RETAINED ON SEQUENTIAL COMBINATION OF VORELOXIN WITH NUCLEOSIDE ANALOGS**

**RESULTS AND DATA ANALYSIS**

24-hour pretreatment with voreloxin, dose-escalation of IC50

**REFERENCES**

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- Lynch et al. ASCO 2000
- Bickert et al. ASCO 2005
- Hime et al. ASCO 2003
- Stockley et al., AACR 2003; Bickert et al., AACR 2005; Hime et al. ASCO 2003, as well as in HLBCC and EOCO (Barka et al. EOCO 2007).