ABSTRACT - UPDATED

Voreloxin (formerly SNS-595) is a potent DNA intercalator and topoisomerase II poison that induces cell cycle dependent DNA damage and rapid apoptosis in cancer cell lines


Background: Voreloxin (formerly SNS-595) is a replication-dependent agent that induces DNA damage, G2 arrest and subsequent induction of apoptosis by selective intercalation of DNA and poisoning of topoisomerase II (Stockett et al.; Hawtin et al., AACR 2008). Voreloxin is under clinical investigation in acute myeloid leukemia and ovarian cancer (Lancet et al., ASH 2007; Zhu, Wenjin Yang, Robert McDowell, Neil Osheroff and Judith A. Fox.  SNS-595 is a potent anti-tumor agent that has a dual mechanism of action: DNA intercalation and site-selective DNA-PK activation (DNA-PK component) is under clinical investigation in acute myeloid leukemia and ovarian cancer (Lancet et al., ASH 2007; γH2AX)

Results: Voreloxin induced dose-dependent DNA damage in G2, S and G1 phase of the cell cycle, whereas G1 cells were markedly less sensitive to the drug. These data were consistent with the selectivity of voreloxin towards proliferating cells. No evidence of DNA damage was observed with the non-intercalative voreloxin analog, consistent with its absence of cytotoxicity. Induction of DNA damage in S phase cells by voreloxin over the concentration range was biphasic: a dose-dependent increase was observed up to 10 µM at 20 µM and beyond, reduced DNA damage was detected. Voreloxin-induced DNA damage activates DNA-PKcs CHK2 and CHK1, consistent with replication foci formation and activation of the checkpoint pathway. At cytotoxic concentrations of voreloxin, apoptosis is induced as indicated by annexin V staining and PARP cleavage. Collectively, the replication-dependent induction of DNA damage by voreloxin is consistent with its activity as a DNA intercalator and topoisomerase II poison. These data also establish the potential of voreloxin towards replicating cells in G2, G1 and G0 phases with cells in G1 being minimally effective.

Conclusions: Voreloxin preferentially induces DNA-damage response in S and G2 phases, where minimal DNA damage is observed in non-replicating (G1) cells. Data are consistent with previous reports correlating voreloxin cytotoxicity with replication phase (Stockett et al., 2005).

SUMMARY & CONCLUSIONS

- Voreloxin preferentially induces DNA-damage response in replicating cells, with damage in M/G2 >> S/G1.
- The induction of DNA damage by voreloxin is consistent with its activity as a DNA intercalator and topoisomerase II poison / inhibitor, in contrast with the damage induced by the non-intercalative topoisomerase II poison, etoposide.
- Voreloxin-induced DNA-damage response implicates the ATM and ATR, consistent with induction of DNA damage in S and M phases of the cycle. These pathways identify potential pharmacodynamic response markers.
- Voreloxin’s mechanism of action derives from its quinoline-like core, consisting of DNA-intercalation and novel inhibition of topoisomerase II that results in site-selective DNA damage and apoptosis.
- While its mechanism of action resembles doxorubicin, key features favorably differentiate voreloxin from the anthracyclines. (1) Voreloxin is not a P-gp substrate, thereby evading the most common tumor resistance mechanism; (2) Voreloxin is active in anthracycline-resistant settings; (3) Voreloxin activity is independent of p53 family proteins; (4) Voreloxin exhibits limited distribution to normal tissues relative to anthracyclines; (5) The chemically less-reactive naphthyridine core produces minimal reactive oxygen species and has lower potential for cardiotoxicity than the anthracyclines.
- These data support the clinical investigation of voreloxin where the anthracyclines are broadly used, including the ongoing Phase 2 studies of voreloxin in AML and platinum-resistant ovarian cancer, and provide rationale for other tumors such as breast cancers.

PDF of this and additional voreloxin publications available at: http://www.sunesis.com/science/presentations_and_publications.php