#2830

Ex Vivo Activity of SNS-595 Against Biopsies of Acute Myeloid Leukemia, Triple Negative Breast and Ovarian Cancers Supports Ongoing and Potential Clinical Indications

Rachael E. Hawtin*, Hannah Mamuszka,^ Michelle R. Arkin* and Judith A. Fox*. *Sunesis Pharmaceuticals, Inc., S. San Francisco, CA and ^ Oncotech Inc., Tustin, CA

Abstract

SNS-595 is a replication-dependent agent that induces DNA damage, irreversible G2 arrest and apoptosis by DNA intercalation and poisoning of topoisomerase II. SNS-595 is under clinical investigation in acute myeloid leukemia and ovarian cancer. Clinical responses have been observed in these indications (Lancet, ASH 2007; McGuire, SGO 2008) and in NSCLC and SCLC (Burris, ECCO 2007). In this study SNS-595 cytotoxicity toward primary patient samples from triple negative (ER / PR / Her-2) breast, ovarian and acute myelogenous leukemia (AML) cancers was determined and compared to other anti-cancer agents. To identify potential patient stratification biomarkers, sensitivity to the agent was correlated with the expression of DNA repair and p53 family proteins.

Cytotoxicity was determined using the Oncotech Extreme Drug Resistance (EDR) proliferation assay. In 20 triple negative breast cancer biopsies SNS-595 activity was compared with doxorubicin and carboplatin. 1μM SNS-595 inhibited proliferation >90% in 13/20 samples (65%) and >80% in 17/20 samples (85%). Activity compared favorably with doxorubicin at clinically relevant concentrations, and 2/4 doxorubicin-resistant samples were sensitive to SNS-595.

Potent anti-proliferative activity of SNS-595 has previously been reported against 17 primary ovarian biopsies (McGuire, EORTC 2007). These data were extended by 3 samples and expanded with expression profiling of the potential sensitivity biomarkers. At clinically relevant concentrations, the activity of SNS-595 compared favorably with platinum, doxorubicin or etoposide; moreover patient samples that were resistant to these agents were sensitive to SNS-595.

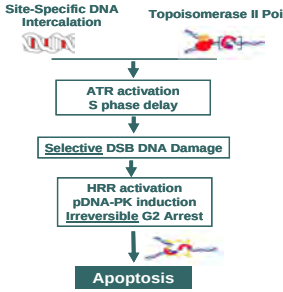
Expression levels of DNA-PKcs and sub-units Ku70 and Ku80 were determined in ovarian samples to test the importance of DNA-PK in repairing SNS-595 induced DNA damage (Hyde et al 2006). Levels of p63 and p73 were also assessed by IHC, having been associated with cisplatin sensitivity in triple negative breast cancers (Leong et al., 2007). Surprisingly, p63 and p73 levels were low or absent in breast and ovarian samples. SNS-595 retained potent activity in the presence of DNA-PK and regardless of the observed levels of p63 and p73.

Initial evaluation of AML patient samples by the CTG proliferation assay showed sensitivity to SNS-595. In conjunction with a Phase 1b study of SNS-595 in combination with cytarabine, baseline bone marrow samples will be evaluated to understand whether *ex vivo* sensitivity is predictive of patient response.

These data demonstrate potent activity of SNS-595 in primary patient samples from triple negative breast, ovarian and AML cancers. SNS-595 compares favorably with doxorubicin, etoposide and platinum therapy at clinically relevant concentrations. These data support the ongoing clinical trials of SNS-595 in ovarian cancer and AML, and support a potential trial of SNS-595 in triple negative breast cancer.

SNS-595 Mechanism of Action

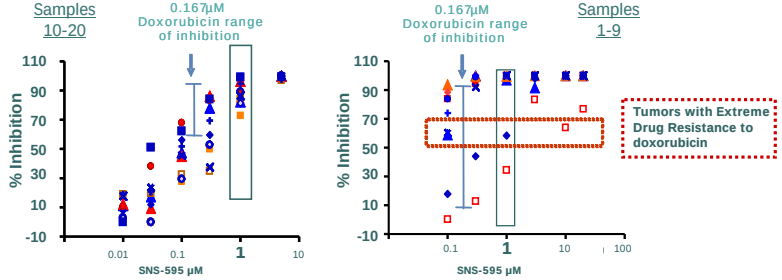
SNS-595 acts by site-specific intercalation of DNA and poisoning of topoisomerase II, leading to site-selective DNA damage, irreversible G2 arrest and apoptosis.



Favorable profile over known topo II inhibitors

- Not a P-gp substrate
- Unaffected by p53 status
- Active in anthracycline- resistant settings
- Lower potential for cardiotoxicity than anthracyclines

SNS-595 is Active in Breast Cancer Biopsies and is Independent of p63 and p73

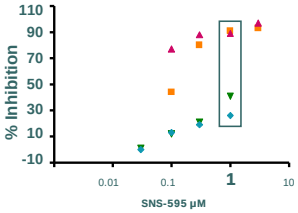


Clinically relevant doses: 1μM SNS-595, 0.1μM doxorubicin

Blue symbols represent samples negative for both p63 and p73
Triple negative breast cancer biopsies: ER-/PR-/HER-2-
Tumors were a mix of sensitive and resistant to platinum

- Activity does not require p53 family members
- SNS-595 is active against doxorubicin –resistant and cisplatin-resistant tumors
- At 1μM SNS-595, proliferation was inhibited >80% in 17/20 samples and >90% in 13/20 samples

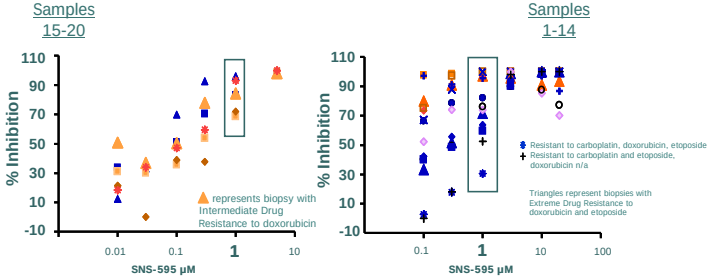
Established SNS-595 Concentrations for Correlative Study in AML



Cell titer Glo proliferation assay

- A dose-range of SNS-595 was tested in AML bone marrow biopsies to identify concentrations to use in correlative study
- 3, 1, 0.3 and 0.1 μM SNS-595 were selected for use in a correlative analysis, linking ex-vivo response to drug with clinical outcome in an ongoing phase1b clinical trial of SNS-595 with cytarabine (AraC)
- Exposures of 1μM SNS-595 for >20 hours were identified as active in the prior phase I single agent study in relapsed/refractory AML

SNS-595 is Active in Ovarian Cancer Biopsies, Including Platinum Resistant Samples



Blue symbols represent carboplatin resistant samples
All samples expressed high levels of DNA-PK
Clinically relevant doses: 1μM SNS-595, 0.1μM doxorubicin

- SNS-595 is active in carboplatin-resistant ovarian tumor biopsies
- SNS-595 is active against ovarian tumor biopsies that are resistant to doxorubicin and / or etoposide
- At 1μM SNS-595, proliferation was inhibited >80% in 11/20 samples and >90% in 7/20 samples
- 1/20 samples was EDR to SNS-595. This sample was also resistant to carboplatin, doxorubicin and etoposide
- Potent activity of SNS-595 continued in the presence of globally high expression of DNA-PK
- 18/20 samples were negative for detection of p63 and p73, with no influence on SNS-595 activity

Summary & Conclusions

- SNS-595 is not a P-glycoprotein substrate and activity is independent of the p53 family.
- SNS-595 is effective in settings where other topoisomerase II posions, such as anthracyclines and etoposide, are ineffective.
  - SNS-595 is active in doxorubicin, etoposide and/or carboplatin-resistant biopsies.
  - Objective responses have been observed in patients with relapsed/refractory AML and platinum-resistant ovarian cancer and who have failed anthracycline-based therapies including "7+3" and Doxil®.
- SNS-595 potently inhibits proliferation of breast and ovarian cancer biopsies at clinically relevant concentrations.
- SNS-595 is in phase 2 trials as a single agent in both platinum resistant ovarian cancer and elderly, untreated AML patients and is in a phase 1b clinical study in combination with cytarabine in relapsed/refractory AML.
- Clinical responses have been observed in relapsed/refractory AML and platinum-resistant ovarian cancers, as well as in lung cancers (ECCO 2007, ASH 2007, SGO 2008).
- The data presented here support the ongoing clinical studies as well as the potential for investigation of SNS-595 in breast cancer.

Additional SNS-595 posters 1859 and 1860
PDF available at: http://www.sunesis.com/science/presentations_and_publications.php