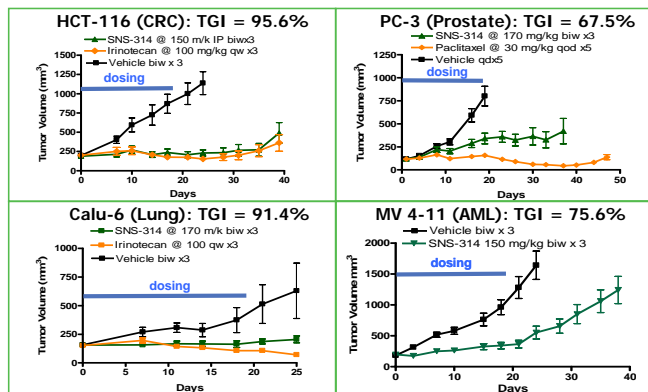


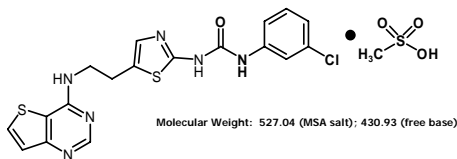
Abstract # 5648

The Aurora family of serine/threonine kinases (Aurora A, Aurora B, and Aurora C) plays a key role in cells orderly progression through mitosis. Elevated expression levels of Aurora kinases have been detected in a high percentage of melanoma, colon, breast, ovarian, gastric, and pancreatic tumors, and in a subset of these tumors the AURKA locus (20q13) is amplified. SNS-314, a novel aminothiazole-derived urea, is a selective inhibitor of Aurora kinases A, B, and C with IC50 values in the low nanomolar range. SNS-314 potently inhibits cell proliferation and induces polyploidy (> 4N DNA) in a diverse panel of human cancer cell lines. In the present study we investigated the pharmacodynamic effects and *in vivo* activity of SNS-314 in human tumor xenograft models. SNS-314 displayed potent anti-tumor activity in HCT-116 (colon), PC-3 (prostate), CALU-6 (NSCLC) and MDA-MB-231 (breast) models. Tumor growth inhibition in these xenograft models ranged from 67.5 to 96.6% on a bi-weekly administration for 3 weeks. Following SNS-314 drug administration, endoreduplication and sustained pro-apoptotic effects measured by increased PARP cleavage and Caspase activation in tumor samples were observed. We also evaluated SNS-314 dependent effects in surrogate tissues as potential biomarkers and indicators of response: inhibition of Histone H3 phosphorylation was observed in bone marrow and skin epidermis obtained from mice after exposure to SNS-314 at drug levels that are efficacious and well tolerated in xenograft models. SNS-314 displays favorable pharmacokinetics with measurable drug levels sustained for more than 96 hours post-dose in the HCT-116 tumor. These drug levels were associated with prolonged inhibition of Histone H3 phosphorylation, an established substrate of Aurora Kinase B. Combined, these data suggest that SNS-314 may be an effective therapeutic agent for the treatment of diverse human malignancies. SNS-314 is currently under investigation in a Phase 1 study for the treatment of patients with solid tumors.

SNS-314 Displays Potent Anti-Tumor Activity in Multiple Xenograft Models

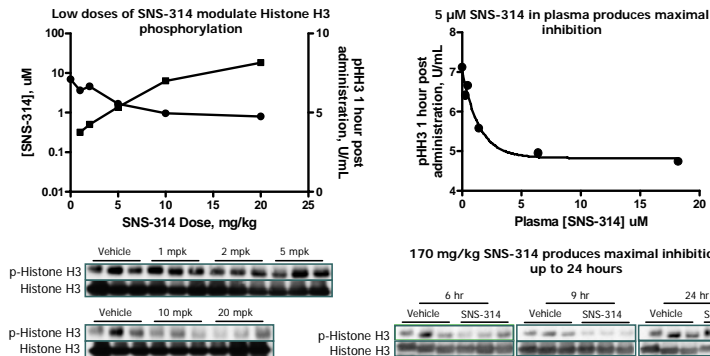


SNS-314 is a Selective Inhibitor of Aurora Kinases

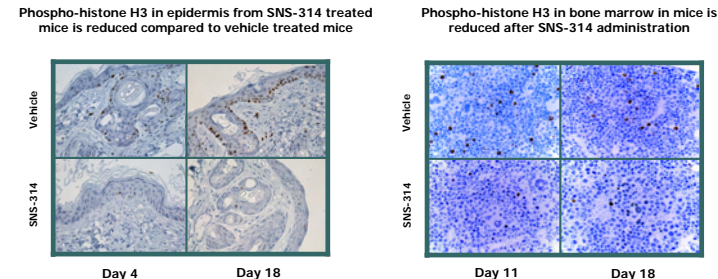


- SNS-314 has an average IC₅₀ of 9 nM for Aurora A, 31 nM for Aurora B, and 3 nM for Aurora C
- SNS-314 binds the active form of Aurora A in an extended conformation
- SNS-314 was tested against a panel of 219 kinases to determine its selectivity profile
 - Seven kinases out of the 219 show an IC₅₀ lower than 100 nM
 - Fourteen kinases had an IC₅₀ value between 100 and 1000 nM
- SNS-314 is a potent inhibitor of cell proliferation (IC₅₀ range 1.8-24.4 nM) and induces polyploidy (>4N DNA) (IC₅₀ range 4.2-9.3 nM) in a diverse panel of human cancer cell lines

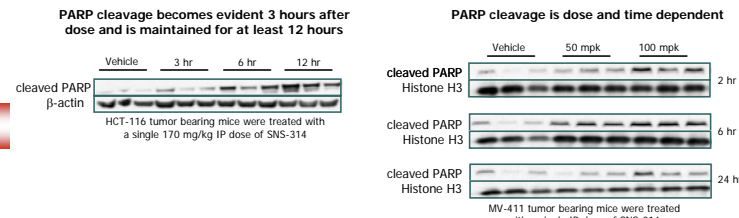
SNS-314 Plasma Concentrations Correlate with Inhibition of Histone H3 Phosphorylation in HCT-116 Tumors



SNS-314 Decreases Histone H3 Phosphorylation in Skin and Bone Marrow



Apoptosis is Induced in Xenograft Tumors After a Single Dose of SNS-314



Conclusions

- Nonclinical pharmacology data strongly support clinical investigation of SNS-314 for treatment of tumors in Phase 1 trials
- SNS-314 is a potent multi-Aurora kinase inhibitor with attractive pharmacologic properties
 - Highly specific Aurora inhibitor
 - Broadly active and well tolerated *in vivo* in several xenograft tumor models using an intermittent dosing schedule
 - Prolonged *in vivo* apoptotic effects
 - Favorable pharmacokinetic properties
 - Antitumor activity consistent with Aurora Kinase inhibition and supported by pharmacodynamic markers in skin and tumors
- The safety and tolerability of SNS-314 is currently being evaluated in a phase 1 dose-escalation clinical trial in patients with advanced solid tumors
ClinicalTrials.gov Identifier: NCT00519662