SNS-595, A NOVEL CELL CYCLE INHIBITOR IN PHASE I CLINICAL TRIALS, CAUSES TUMOR REGRESSIONS, CELL-CYCLE ARREST, AND APOPTOSIS IN MURINE MODELS OF CANCER

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**ABSTRACT #2277**

**BIOLOGIC ACTIVITY OF SNS-595 IN HCT116 TUMORS**

SNS-595 is a novel cell cycle modulator currently in clinical trials for the treatment of advanced solid malignancies. SNS-595 shows antitumor activity in a broad spectrum of murine xenograft and human autologous tumor models, including drug-resistant models. Studies in cell culture and xenografts show that SNS-595 induces phosphorylation of key checkpoint proteins, cell cycle arrest, and apoptosis in cancer cells. A single dose of SNS-595 elicits sustained and irreversible arrest in G2/M phase, and results in tumor regression and cures in the highly metastatic syngeneic Colo-26 tumor model known to be refractory to many of the major classes of cytotoxic drugs. SNS-595 is highly active on all schedules with complete regressions and cures when dosed at the MTD of 20 mg/kg. When dosed at 1/2 the MTD, the weekly and biweekly regimens still result in cures, whereas a reduction of the cumulative effect was apparent with the least frequent regimen.

**METHODS**

All in vivo studies were performed in accordance with IACUC guidelines and in harmony with the Guide for Laboratory Animal Care and Use. Inhibition of cell cycle and apoptosis markers were measured by the appearance of cell cycle checkpoint proteins measured by their phosphorylation and p13 phosphorylation, as well as activation of apoptotic markers measured by the appearance of p21 and p13 phosphorylations. The responses in tumors are rapid and consistent with those observed in cell cultures.

**RESULTS**

**TIME COURSE OF SNS-595 PATHWAY ACTIVATION (20 mg/kg DOSE, n=4)**

**TUMOR AND PLASMA LEVELS AFTER 20 mg/kg IV DOSE**

SNS-595 shows good tumor/plasma ratios and tumor concentrations above 10x the cellular GI50 (2560 nM or 1000 ng/mL) for 16 hr. Tumor Site: Tumor Site: SNS-595 shows excellent distribution to tumor tissue resulting in tumor to plasma ratios of >10 in the tumor models tested.

**CONCLUSIONS**

- **SNS-595** shows excellent distribution to tumor tissue resulting in tumor to plasma ratios of >10 in the tumor models tested.
- **SNS-595** shows biological activities consistent with those observed in cell culture analysis of cell cycle markers in HCT-116 tumors, with maximum activation 2 to 16 hr post dose.
- **Activation of apoptosis markers in HCT-116 tumors, with maximum activation 4 hr post dose**.
- Stress signals observed in vitro lead to vivo activity.

Precipitously, SNS-595 retains curative effects in the highly metastatic syngeneic Colo-26 tumor model, even when dosed every three weeks.

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**CURES IN COLO-26 SYNGENEIC MODEL WITH SPARSE DOSING**

SNS-595 shows tumor regression and cures in the highly metastatic syngeneic Colo-26 tumor model known to be refractory to many of the major classes of cytotoxic drugs. SNS-595 is highly active on all schedules with complete regressions and cures when dosed at the MTD of 20 mg/kg. When dosed at 1/2 the MTD, the weekly and biweekly regimens still result in cures, whereas a reduction of the cumulative effect was apparent with the least frequent regimen.