SNS-595 potentiates the *in vivo* anti-tumor activity of carboplatin, cisplatin, and gemcitabine in solid tumor xenografts.

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ABSTRACT #659

SNS-595 is under clinical investigation in acute leukemia and ovarian cancer. Clinical responses have been observed in these indications, as well as in non-small cell (NSCLC) and small cell lung cancers. SNS-595 is a replication-dependent DNA damaging agent that causes irreversible G2 arrest, and rapid apoptosis. A secondary mechanism for SNS-595 is a unique inhibition of topoisomerase II that causes highly selective DNA damage with low dependence on topoisomerase II for its potent anti-tumor activity. The identification of new anti-cancer agents to be used in combination with established cancer therapies is a key step in the development of new treatment modalities. Studies in culture have shown that SNS-595 combines synergistically with established chemotherapeutic agents (Wright et al., *Proc Amer Assoc Cancer Res* 47: 2132, 2006). Extending these findings to in vivo studies, we have shown that SNS-595 acts synergistically with cytarabine, the standard of care in acute myeloid leukemia (AML), to ablate bone marrow (Arbitrario et al., *Blood {ASH Annual Meeting Abstract}* 108: 2321, 2006). These studies have led to investigation of SNS-595 in combination with cytarabine clinically in AML patients. In the current study, we examine the potential of SNS-595 to combine effectively with carboplatin, cisplatin, and gemcitabine in vivo in several solid tumor xenograft models. SNS-595, cisplatin, carboplatin and gemcitabine were administered alone or in combination to athymic nude mice bearing subcutaneous H460 NSCLC tumors or A2780 ovarian carcinoma tumors. Treatments were initiated when mean tumor volume was greater than or equal to 100 mm^3. The animals were monitored for tumor growth and assessed for tolerability of the different treatment regimens. In the H460 NCSLC model, administration of SNS-595 (10 mg/kg IV qw x5) in combination with carboplatin at 75% of its maximum tolerated dose (MTD, 75 mg/kg IP qw x3) induced significant tumor growth inhibition (TGI) of 75% compared to 32% for carboplatin alone. Similarly, in the A2780 model of ovarian carcinoma, SNS-595 (10 mg/kg IV qw x3) combined with cisplatin at its MTD (5 mg/kg IP qw x3) resulted in a TGI of 64% compared to 49% for single agent cisplatin. In the H460 NCSLC model, the combination of SNS-595 (10 mg/kg IV qw x3) with gemcitabine at 75% of its MTD (75 mg/kg IP biw x2) results in an 82% TGI and 51 day tumor growth delay compared to 37% TGI and a 5 day tumor growth delay for single agent gemcitabine. Body weight losses of 8%, 14% and 8% were observed for the SNS-595/carboplatin, cisplatin and gemcitabine combinations, respectively, indicating that the dosing regimens were well tolerated. The results from these studies clearly demonstrate that SNS-595 combines effectively with platinum compounds or anti-metabolites such as gemcitabine, and support clinical exploration of SNS-595 in combination with these established chemotherapeutic agents.

METHODS

STUDY DESIGN

•Cell Lines

- 5 x 10^6 A2780 ovarian carcinoma or H460 NSCLC cells in a 50:50 mixture of matrigel and PBS were implanted sc in the hind flank of female nu/nu mice.
- 5 x 10^6 BxPC-3 pancreatic carcinoma cells in a 50:50 mixture of matrigel and PBS were implanted sc in the hind flank of male NIHIII mice.
- Mice were randomized into treatment groups after tumors reached 100- 250 mm^3.

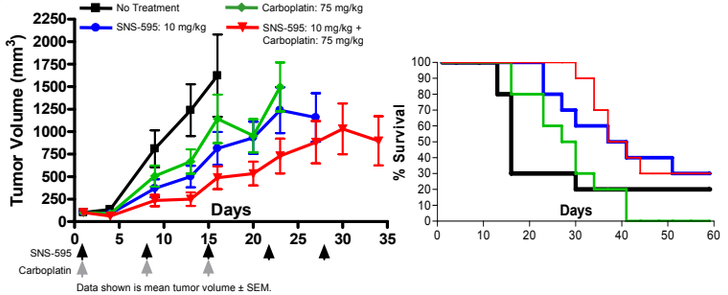
•Treatments

- SNS-595: 10 and 15 mg/kg IV qw x 3 or 5 (50% and 75% of MTD)
- Carboplatin: 75 mg/kg IP qw x 3 (75% of MTD)
- Cisplatin: 5 mg/kg IP qw x 3 (MTD)
- Gemcitabine: 75 and 65 mg/kg IP biw x 2 (75% and 81% of MTD in H460 and BxPC3 models, respectively)

CALCULATIONS

- Acceptable toxicity is defined as a mean group weight loss of 15% or less.
- Time to Endpoint (TTE) is defined as: the time elapsed for an animal to be removed from the study due to a tumor volume >2000 mm^3 or body weight loss of >20%.
- Anti-tumor activity was assessed when the vehicle group was reduced to <75% due to the removal of animals from the study as defined by TTE.
- Tumor volume (TV) was calculated as: L x W^2 x 0.52, except for the A2780 xenograft with cisplatin which was calculated as: L x W x H x 0.52.
- Tumor Growth Inhibition is defined as: $\frac{(TV_{veh}\ \text{Day}\ x - TV_{veh}\ \text{Initial}) - (TV_{tx}\ \text{Day}\ x - TV_{tx}\ \text{Initial})}{(TV_{veh}\ \text{Day}\ x - TV_{veh}\ \text{Initial})} \times 100\%$
- Tumor Growth Delay is defined as: median of TTE_{tx} – median of TTE_{veh}
- A two-tailed student t-test was used for statistical analysis of tumor growth inhibition. A log-rank test was used for statistical analysis of survival.
- All experiments were performed in accordance with protocols approved by the Sunesis Pharmaceuticals, Inc. Institutional Animal Care and Use Committee and in accordance with local and Federal Regulations.

SNS-595 AND CARBOPLATIN INHIBIT NSCLC XENOGRAFT GROWTH

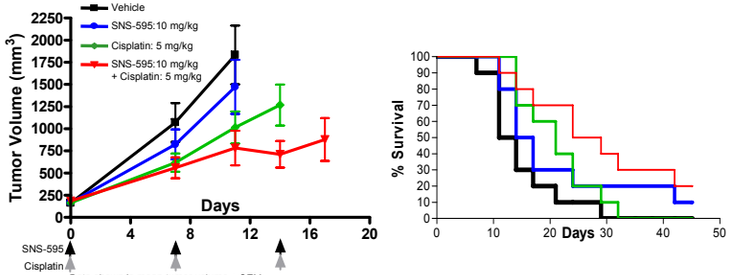


Data shown is mean tumor volume ± SEM.

Group	BW Nadir (Day of)	% Tumor Growth Inhibition (Day 16)	Tumor Growth Delay (days)
SNS-595 10 mg/kg qw x 5	-0.7% (Day 4)	53.2% (p>0.05)	23.0
Carboplatin 75 mg/kg qw x 3	-2.8% (Day 16)	31.6% (p>0.05)	12.5
Combination	-8.0% (Day 4)	**74.6% (p<0.05)**	**23.0**

SNS-595 combined with carboplatin significantly delays tumor growth and enhances survival of mice bearing H460 NSCLC tumors compared to single agent carboplatin.

SNS-595 AND CISPLATIN INHIBIT OVARIAN CANCER XENOGRAFT GROWTH

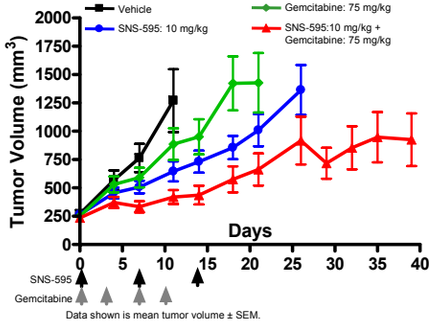


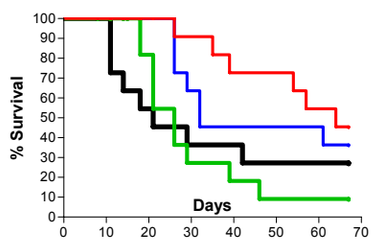
Data shown is mean tumor volume ± SEM.

Group	BW Nadir (Day of)	% Tumor Growth Inhibition (Day 11)	Tumor Growth Delay (days)
SNS-595 10 mg/kg qw x 3	-4.7% (Day 4)	21.7% (p>0.05)	3.5
Cisplatin 5 mg/kg qw x 3	-10.9% (Day 11)	49.0% (p<0.05)	9.0
Combination	-14.1% (Day 11)	**64.2% (p<0.05)**	**14.0**

SNS-595 combined with cisplatin delays tumor growth and significantly enhances survival of mice bearing A2780 Ovarian tumors compared to single agent cisplatin.

SNS-595 AND GEMCITABINE SIGNIFICANTLY INHIBIT NSCLC XENOGRAFT GROWTH



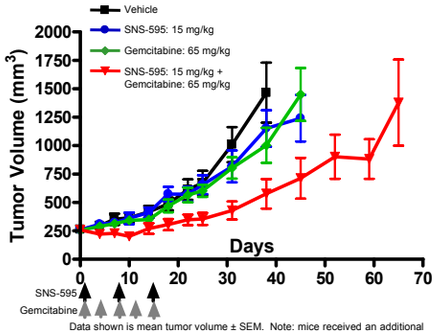


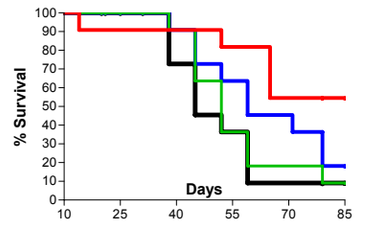
Data shown is mean tumor volume ± SEM.

Group	BW Nadir (Day of)	% Tumor Growth Inhibition (Day 11)	Tumor Growth Delay (days)
SNS-595 10 mg/kg qw x 3	-5.9% (Day 11)	61.9% (p<0.05)	11.0
Gemcitabine 75 mg/kg biw x 2	-7.4% (Day 11)	36.6% (p>0.05)	5.0
Combination	-7.9% (Day 11)	**81.7% (p<0.01)**	**51.0**

SNS-595 combined with gemcitabine significantly delays tumor growth and enhances survival of mice bearing H460 NSCLC tumors compared to single agent gemcitabine.

SNS-595 AND GEMCITABINE SIGNIFICANTLY INHIBIT PANCREATIC CANCER XENOGRAFT GROWTH





Data shown is mean tumor volume ± SEM. Note: mice received an additional dose of gemcitabine.

Group	BW Nadir (Day of)	% Tumor Growth Inhibition (Day 38)	Tumor Growth Delay (days)
SNS-595 15 mg/kg qw x 3	-2.5% (Day 21)	25.9% (p>0.05)	23.0
Gemcitabine 65 mg/kg biw x 2	0% (Day 0)	20.2% (p>0.05)	12.5
Combination	-9.9% (Day 21)	**71.5% (p<0.01)**	**>40.0***

* Study ongoing

SNS-595 combined with gemcitabine significantly delays tumor growth and enhances survival of mice bearing BxPC-3 pancreatic tumors compared to single agent gemcitabine.

SUMMARY

- Combinations of SNS-595 with carboplatin, cisplatin, and gemcitabine demonstrate potent anti-tumor activity resulting in increased long term survival of mice bearing xenograft tumors.
- Combined with our understanding of the mechanism of action, these data support clinical investigation of SNS-595 in rational combination studies in solid tumors.
- SNS-595 is being investigated in clinical studies of acute leukemias and ovarian cancer. Clinical responses with single agent SNS-595 have been seen in these indications (EORTC abstract #A158 for ovarian study results), as well as in non-small cell and small cell lung cancers.