Sensitivity to SNS-595 is Related to Activation of Double Strand DNA Break Repair Pathways Including Homologous Recombination

Rachael E. Hawtin, David Stockett, Robin A. Kimmell, Erik Eversen, Di Kwan Wong, Pietro Taverna and Judith A. Fox

Sunesis Pharmaceuticals, Inc., S. San Francisco, CA

ABSTRACT

SNS-595 is a replication-dependent agent that induces DNA damage, irreversibly G2 arrest and apoptosis by inhibition of DNA synthesis and induction of replication stress. SNS-595 is under clinical investigation in a variety of cancer indications. Several mechanisms have been proposed to explain SNS-595 activity including the inhibition of DNA topoisomerase II, arrest of S phase cells, and induction of double-strand DNA breaks (DSB), which are repaired by two major pathways: non-homologous end joining (NHEJ) and homologous recombination (HRR). DSBs repair is essential for cell survival and is central to many biological processes. DSB repair is mediated by different pathways depending on DNA damage character and cell type.

We report here SNS-595-induced DNA damage is efficiently repaired by HRR, and cells deficient in HRR are sensitized to the agent. The DNA damage induced by SNS-595 is repaired by HRR, and cells deficient in HRR are sensitized to the agent. The DNA damage induced by SNS-595 is repaired by HRR, and cells deficient in HRR are sensitized to the agent. The DNA damage induced by SNS-595 is repaired by HRR, and cells deficient in HRR are sensitized to the agent.

SUMMARY & CONCLUSIONS

> SNS-595 targets replicating DNA and cytotoxicity correlates with cell proliferation rate
> The DNA damage induced by SNS-595 is repaired by HRR, and cells deficient in HRR are sensitized to the agent
> Breast and ovarian cancers with BRCA mutations may represent highly sensitive sub-population
> Clinically achievable exposures of SNS-595 are able to overwhelm the HRR damage response
> Broad activity has been seen in primary breast cancer biopsy samples (Poster #2830)
> Clinical responses to SNS-595 have been observed in relapsed / refractory AML and platinum-resistant ovarian cancers, as well as in lung cancers (ECCO 2007, ASH 2007, SGO 2008).
> SNS-595 is currently in a clinical phase 1b trial in relapsed / refractory AML in combination with cytarabine, and in phase 2 trials as a single agent in both platinum-resistant ovarian cancer and in elderly, untreated AML patients.

Additional SNS-595 posters:  1860 and 2830