

Phase I study of ON 01910.Na, a novel polo-like kinase 1 pathway modulator, administered as a weekly 24-hour continuous infusion in patients with advanced cancer.

Sub-category: [Phase I Studies](#)

Category: Developmental Therapeutics: Cytotoxic Chemotherapy

Meeting: [2008 ASCO Annual Meeting](#)

Abstract No: 2515

Citation: *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 2515)

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Abstract:

Background: ON 01910.Na induces G2/M cell cycle arrest, apoptosis, and cell death in a broad spectrum of cancer cells, but not in non-neoplastic cells. In vitro, cell killing is dependent on drug exposure time. Based on these preclinical findings, a weekly 24hr continuous infusion (CI) study to determine safety and MTD of ON 01910.Na was initiated. **Methods:** Patients with advanced cancers received ON 01910.Na as a weekly 24hr CI. Dose cohorts ranged from 250-2750 mg/m² based on a modified Fibonacci escalation algorithm using the accelerated titration scheme (NCI). Intra-patient dose escalation was allowed. Intensive and comprehensive plasma sampling was performed at weeks 1 and 4 or 8 to determine drug pharmacokinetics. **Results:** 23 pts (7:16 M:F, 45-80 yrs) have received ON 01910.Na. At the max dose (2750 mg/m²), 3 pts have received 6, 3 and 2 wks of 24-hour CI therapy. The median (range) wks of CI delivered was 6 (2 - 36). Grade 2 toxicities (2-grade increase over baseline) included fatigue (3 pts) and anorexia (1 pt). Fatigue (11/23 pts) was the most common side effect, with no grade 3 or greater fatigue observed. Overall, three grade 3 events occurred, none of which were drug-related. The best response was a pt with advanced ovarian cancer who maintained stable disease for 36 wks of treatment. Plasma concentrations of ON 01910.Na reach a steady state within 3 hrs of starting infusion, and decline rapidly after the end of infusion. The drug has a half-life of about 2 hrs, with clearance decreasing and drug exposure (AUC) increasing non-linearly as dose increases. Mean steady state plasma concentration at the max assessed dose of 2,750 mg/m² was 52.8 ± 7.3 µg/ml, well in excess of drug concentrations shown to be cytotoxic to several cancer cell-lines in vitro, including cell-lines widely resistant to chemotherapeutics. **Conclusions:** ON 01910.Na is well tolerated as a weekly 24h continuous infusion. In the dose range studied, the drug exhibited non-linear kinetics with rapid attainment of plasma concentrations that are cytotoxic to cancer cells in vitro, but have limited end-organ toxicity in vivo. Study data continues to accrue, and we expect to recommend a phase II dose shortly. Further analysis and combination phase I studies are planned.

[Abstract Disclosures](#)

Associated Presentation(s):

1. Phase I study of ON 01910.Na, a novel polo-like kinase 1 pathway modulator, administered as a weekly 24-hour continuous infusion in patients with advanced cancer.

Meeting: [2008 ASCO Annual Meeting](#)

Presenter: [Jeffrey M Vainshtein, BA](#)

Session: [Developmental Therapeutics: Cytotoxic Chemotherapy](#) (Poster Discussion)



In vitro comparative efficacy of ON01910.Na and cisplatin with radiation on cervical carcinoma cells.

Sub-category: [Uterine Cancer](#)

Category: Gynecologic Cancer

Meeting: [2008 ASCO Annual Meeting](#)

Abstract No: 16565

Citation: *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 16565)

Author(s): L. Agoni, I. Basu, A. Danish, E. P. Reddy, A. Alfieri, C. Guha, G. L. Goldberg

Abstract:

Background: A synthetic benzyl styryl sulfone (ON01910.Na) has been shown to have anti-tumor activity, alone and in combination with other chemotherapeutic agents as a Chk2 inhibitor and anti-mitotic agent that induces selective G2/M arrest followed by apoptosis in several cancer cell lines. It is now undergoing phase 1-2 clinical trials. Cisplatin is the preferred primary chemotherapy for cervical malignancies. Studies were initiated to test if ON01910.Na may be used on checkpoint-compromised tumor to enhance the cytotoxic effects of radiation therapy. The primary objective of this study was to evaluate whether ON01910.Na has a more effective radiosensitizing capacity than Cisplatin. **Methods:** Clonogenic survival assay on HeLa cells incubated for 24 hours with ON01910.Na (1 μ M) or Cisplatin (1 μ M), prior to irradiation (2-8 Gy). FACScan cytometry was used for cell cycle analysis. **Results:** IC₅₀ values for ON01910.Na and Cisplatin were 0.1 and 1 μ M respectively. FACS analysis demonstrated G2/M blocked cells at the concentrations used for this clonogenic assay for ON01910.Na. Survival curve comparison revealed a survival fraction of 30% for Cisplatin and 10% for ON01910.Na, and a radiosensitization effect of 1.1 for Cisplatin and 2.0 for ON01910.Na. Two-ways ANOVA analysis for each radiation dose subset showed that survivals among treatment groups were significantly different ($p < 0.0001$). **Conclusions:** Our data suggest that ON01910.Na appears to be more effective than Cisplatin when combined with radiation. The low toxicity on normal cells in culture and this reported data supports the need for clinical trials with ON01910.Na for patients with cervical carcinoma.