

## Phase I study of ON 01910.Na by 3-day continuous infusion (CI) in patients (pts) with advanced cancer.

Sub-category: [Other Novel Agents](#)

Category: Developmental Therapeutics: Molecular Therapeutics

Meeting: [2006 ASCO Annual Meeting](#)

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### Abstract No: 13137

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**Abstract:** **Background:** The benzyl styryl sulfone analog ON 01910.Na is a novel anticancer agent that inhibits mitotic progression and induces apoptosis; it has activity against most human cancer cells *in vitro* and against a broad spectrum of human xenografts in mice. Cell kill effects are exposure time-dependent *in vitro*. After 3d exposure 200nM ON 01910.Na killed > 90% of Daudi lymphoma cells, whereas 40-fold higher drug concentration killed only 50% of cells after 24h exposure. Dogs that received CI of 325mg/kg/d x3 failed to reach MTD. **Methods:** Starting dose 50mg/m<sup>2</sup>/d as a 72hr CI was 1/10<sup>th</sup> MTD of rats' daily dose given x 28d. Treatment cycles were repeated every 2wks until progressive disease, intolerable toxicity, or withdrawal of consent. Dose was escalated by Fibonacci progression in single pts until grade 2 toxicity when cohorts of 3 are to be studied. Volunteers may be retreated at a higher dose if tolerated by a preceding naïve subject. **Results:** One man and four women (61-77 yrs) have been studied in 21 cycles in 5 mos as of 1/10/06. Doses of 50, 100, 150 and 250mg/m<sup>2</sup>/d x 3 have been given for 1 to 10 cycles. Grade 1 granulocytopenia (2/4 pts with carcinoma) indicates biologic activity. Grade 1 fatigue (3/5) was less than in prior chemotherapy regimens. No grade 2 toxicity has yet occurred. Cumulative toxicity has not been seen. Two pts have had stable disease 6+ and 22+ wks. After deproteinization with acetonitrile, plasma or serum samples were measured by mass spectrometry. At 100mg/m<sup>2</sup>/d steady state levels were 730nM after the 1st cycle and 1190nM after the 4th cycle. Drug levels were maximal at 3 to 6h despite CI suggesting induction of a metabolizing pathway. Levels fell precipitously at the end of infusion on the 1<sup>st</sup> cycle but a low level persisted in one pt for 48h after the major drop in the 4<sup>th</sup> cycle, suggesting drug accumulation. **Conclusion:** Levels effective *in vitro* have been obtained *in vivo* by CI without limiting toxicity. Hints of activity already seen suggest that this compound has clinical promise. This phase I study continues.

## Phase I study of ON-01910.Na, a novel cell cycle inhibitor in adult patients with solid tumors.

**Sub-category:** [Other Novel Agents](#)

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**Author(s):** R. C. Donehower, A. Jimeno, J. Li, K. Galvin, F. Anthony, R. Reddy, P. Reddy, W. Messersmith, D. Laheru, S. D. Baker

**Abstract:** **Background:** ON-1910.Na is a new chemical entity, novel cell cycle inhibitor which arrests cells in G<sub>2</sub>/M, affects phosphorylation of several regulatory kinases and lacks cross resistance to other standard chemotherapy agents. This is a first-in-man Phase I dose escalation study to determine the dose limiting toxicities, recommended Phase II dose, and pharmacokinetic (PK) profile, and to document any antitumor activity of ON-01910.Na. **Methods:** Patients had histologically confirmed solid tumors refractory to standard therapy. ON-1910.Na, formulated as a solution in PEG400, was administered as a 2-hour infusion on days 1, 4, 8, 11, 15, and 18 followed by a 10 day observation period for a total of 28 days per cycle. The initial dose was 80 mg and was escalated using an accelerated titration schedule; one patient was treated per cohort until grade 2 toxicity was documented. A dose confirmation cohort of up to 12 patients will be treated at the maximum tolerated dose (MTD). A comprehensive PK study was performed on days 1 and 15 of the first cycle, plus trough samples were collected. **Results:** Thirteen patients (7F, 6M; ages 46-73) have received 20 cycles. Dose levels of 80, 160, 320, 480, 800, 1280, 2080, and 3120 mg were evaluated in 8 patients, and a further dose of 4370 mg has been evaluated in 5 patients. Toxicities have been anemia (2 G1, 1 G2), leucopenia (1 G1, 1 G2), hyperglycemia (2 G1), elevated AST/ALT (1 G1, 1 G2), nausea (3 G1), diarrhea (3 G1), skeletal pain (5 G1, 1 G2), abdominal pain (2 G1), tumor pain (1 G2), and fatigue (3 G1, 1 G2), and have clustered at the latter 3 dose levels. PK analysis shows increasing ON-1910.Na exposure with increasing doses. ON-1910.Na has a low clearance (13 L/h), long half-life (20 h), distribution in excess of blood volume (58 L) and PK parameters are similar on days 1 and 15. Approximately 3-fold and 5-fold inter-subject variation in ON-1910.Na clearance was observed on days 1 and 15, respectively. No antitumor activity has been documented by standard criteria. **Conclusions:** Dose escalation is continuing.