

Abstract #80933

Final results of a phase 1 study of the combination of a novel cell cycle inhibitor ON 01910.Na with gemcitabine in patients with advanced pancreatic and other solid tumors.

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Background: ON 01910.Na (ON) is a novel multi-targeted inhibitor of several regulatory pathways including polo-like kinase 1 (Plk1) and PI-3 kinases, with synergistic preclinical activity when combined with gemcitabine (G) (Jimeno et al, 2008, 2009), prompting a phase 1 clinical evaluation.

Methods: Patients (pts) had histologically confirmed solid tumors refractory to standard therapy. G was administered as a 30-min infusion on days 1, 8 and 15 of a 28-day cycle. ON was administered as a 2-h infusion on days 1, 4, 8, 11, 15, and 18. Assessments included safety, response, pharmacokinetic interaction studies at the MTD, and pharmacodynamics in tumor at the MTD. The MTD was further confirmed in an expansion cohort enriched in advanced pancreatic cancer pts.

Results: Thirty-six pts (median age 61; median ECOG PS 1) received a median of 3 cycles (6 pts ongoing) at 5 dose levels: (G/ON mg/m²: 750/600 n=6; 1000/600 n=5; 750/1200 n=3; 1000/1200 n=3; 1000/1800 n=19). Only those toxicities that were expected from G were observed in patients treated with the combination, and included thrombocytopenia, neutropenia, elevated AST/ALT, nausea, vomiting, and fatigue. One DLT was documented (death at Day 18 at the 1800 mg/m² ON dose). Antitumor activity was seen in one G-pretreated Hodgkin's lymphoma pt (PR), 2 ovarian cancer pts (1 G-pretreated with 50% decrease in CA125; 1 G-naïve with 50% decrease in CA125 and 12% tumor regression), one NSCLC pt (SD at 24 weeks) and one thymic cancer pt (PR at 32 weeks). Additionally, 18 advanced pancreatic cancer (PC) pts were enrolled. Tumor regression (including one confirmed PR in a G-pretreated pt) was noted in 7/13 evaluable pts and CA 19-9 decrease in 8/13 pts. Median progression-free survival was 19 weeks and overall survival 48 weeks at 1200 and 1800 mg/m² ON doses (n=12) in the subset of 16 metastatic PC pts, 11 of whom were previously treated with G.

Conclusions: ON 01910.Na 1800 mg/m² and gemcitabine combination is well tolerated. Anti-tumor activity in G-pretreated pts with advanced PC provide the rationale for a phase 2 evaluation in metastatic PC pts. Final results will be presented and molecular data including PI3K mutation status.

Abstract #80890

Final results of a phase 1 dose-escalation study of ON 01910.Na in combination with oxaliplatin in patients with advanced solid tumors.

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Background: ON 01910.Na is a novel multi-targeted inhibitor of several regulatory pathways including polo-like kinase 1 (Plk1) and PI-3 kinases, with synergistic nonclinical activity when combined with oxaliplatin, prompting phase I clinical evaluation.

Methods: Patients with advanced cancer received escalating doses of ON 01910.Na as 24hr weekly continuous infusions. Oxaliplatin was administered biweekly as a $85\text{mg}/\text{m}^2$, 2 hr infusion. The ON 01910.Na dose cohorts ranged from 250-1350 mg/m^2 based on a modified Fibonacci escalation algorithm using the accelerated titration scheme (NCI). Inpatient dose escalation was allowed.

Results: Thirty patients (pts) (22 females; ages: 29-80 yrs received an overall mean 9.4 (range=1-30) number of weeks of combination therapy: ON 01910.Na mg/m^2 : 250 n=10; 650 n=9; 1050 n=8; 1350 n=3. No dose limiting toxicity was observed in any patient. Grade 3+ toxicities included pain (3 pts), lethargy & weakness (1 pt), pneumonia (1 pt), hyponatremia (1pt), anemia (1pt), transient ischemic attack (1pt), vomiting (1pt), urinary tract infection (1pt), shortness of breath & myocardial infarction (1pt). Confirmed partial response was observed in 1 pt with chemotherapy-refractory ovarian cancer (duration = 11 wks) and in another pt with metastatic breast cancer (duration = 13 wks). Stable disease was observed in 4 pts with colon cancer (42 wks and 12 wks), ovarian and renal cancer (12 wks).

Conclusions: ON 01910.Na administered as a 24hr infusion in combination with oxaliplatin was well tolerated and resulted in objective tumor responses in advanced ovarian, breast, colon and renal cancer.