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A novel phosphoramidate ProTide (NUC-1031) overcomes acquired and intrinsic resistance to gemcitabine.

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Background: Resistance to gemcitabine is a major problem in the treatment of cancer. The key resistance mechanisms associated with gemcitabine are: lack of nucleoside transporters; lack of kinases for phosphorylation; and/or, rapid metabolism by deaminases. Resistance results in complete response rates of less than 10% in pancreatic cancer. The addition of a phosphoramidate ProTide moiety to gemcitabine enables: passive entry into the cell, by-passing the reliance on transporters; reduced reliance on kinases for phosphorylation; and, less susceptibility to deamination.

Methods: The ProTide (NUC-1031) was compared to the parent molecule (gemcitabine) in two pancreatic tumor xenograft models: Mia-Pa-Ca-2 (n=40), which is partially responsive to gemcitabine; and BxPC-3 (n=40), which is resistant. Two dose regimens for each tumor type were used, with NUC-1031 administered IP at doses of 0.076 or 0.19 mMol/kg when tumors had reached 150 - 200mm³. The objective was to determine the ability of a novel agent (NUC-1031) to overcome gemcitabine resistance by measuring tumor growth in partially responsive and resistant pancreatic cell lines.

Results: The anti-tumor effect of NUC-1031 was greater and longer lasting than that of gemcitabine and control in both cell lines. NUC-1031 inhibition of tumor growth was significantly different from control in Mia-Pa-Ca-2 on days 4, 11, 14, 18, 21 & 25, and in BxPC-3 cells on days 25, 29, 33 and 37. In Mia-Pa-Ca-2 the tumor volume decreased immediately after first dosing and held at low levels until the end of the experiment. NUC-1031 was well tolerated and animals lost <2% body weight on treatment and this was regained rapidly after cessation of treatment. **Conclusions:** NUC-1031 showed statistically significant reduction in pancreatic tumor volume compared with gemcitabine and control. A phase I/II study of NUC-1031 in resistant/refractory pancreatic cancer is scheduled.