The potent quadruplex-binding compound QN-302 shows anti-tumor activity in patient-derived *in vivo* models of pancreatic cancer

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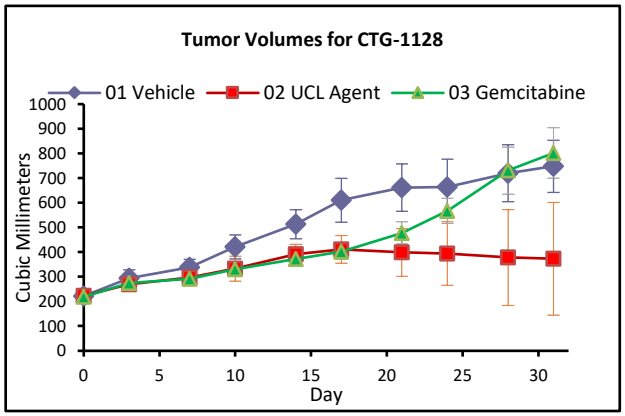
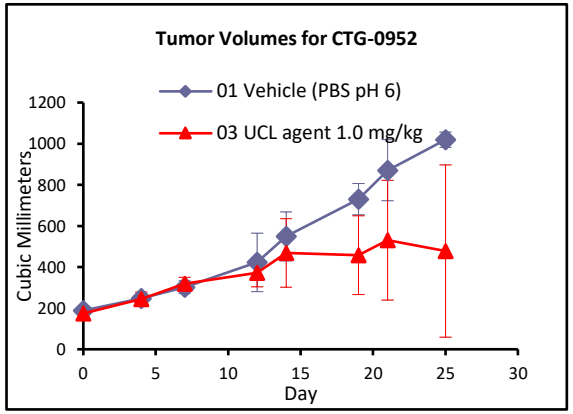
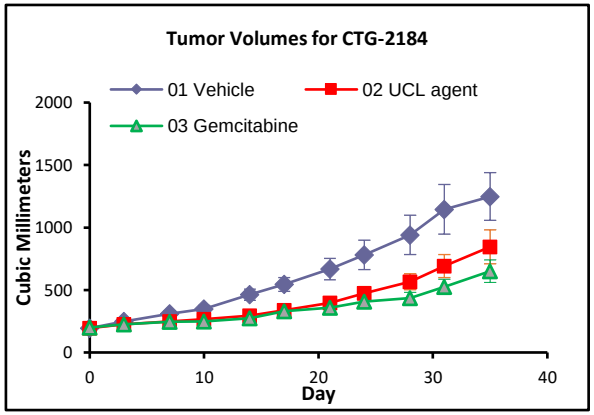
The compound QN-302, a tetra-substituted naphthalene diimide derivative has been previously disclosed to have single-digit nM anti-proliferative activity in a panel of human pancreatic ductal adenocarcinoma (PDAC) cell lines (Ahmed *et al*., *ACS Med Chem Lett*, 2020, **11**, 1634-1644 and significant anti-tumor activity in the MIA-PACA2 xenograft model for PDAC as well as in the more demanding KPC model.

We now report that this compound also shows significant anti-tumor activity in three patient-derived xenograft (PDX) models for PDAC.

Immunocompromised mice were implanted subcutaneously with tumor fragments from one of the pancreatic models into the left flank. After tumors grew to 150-300 mm^3, mice (n = 7/group) were intravenously administered BIWx4 with vehicle, UCL Agent at 1, 1.5 or 2 mg/kg or gemcitabine at 15 mg/kg. Effects on tumor growth were evaluated by measuring % tumor growth inhibition Tolerability was assessed by body weight loss, lethality, and clinical signs of adverse treatment-related side effects. Tumor volumes and body weights were measured twice a week. (PDX tumor studies undertaken under contract by Champions Oncology).







Details of the tumors from which the QN-302 responsive PDX models were derived

PDX Model	Tumor status	Diagnosis	Disease stage	Gender	Gemcitabine patient	Gemcitabine PDX
CTG-1128	Primary	First diagnosis	I	Female	Responded	Responded
CTG-2184	Metastatic	Not available	IV	Male	Resistant	N/A
CTG-0952	Metastatic	Not available	IV	Female	N/A	N/A

Compound QN-302 was well-tolerated in all the six models evaluated. Overall, 3/6 models did not show significant changes in tumor growth. No consistent pattern of QN-302 responsiveness with respect to disease stage, gender or tumor status was observed. These difficulties may reflect limitations for several of the models, in that clonal evolution may alter the original patient tumor characteristics. This is likely to be the cause of contrasting gemcitabine responses in patient and PDX, as observed in models CTG-1128 and 2184. No diagnostic abnormalities were observed in histopathological examinations of heart and brain tissue from treated animals.

The quadruplex-targeting compound QN-302 shows significant activity in several PDX models for pancreatic cancer, as well as significant activity in xenograft models and the genetic KPC model, together with good tolerance and bio-availability at therapeutic doses. QN-302 is currently in pre-clinical development with Qualigen Therapeutics Inc