The potent quadruplex-binding compound QN-302 shows potent anti-proliferative activity in a prostate cancer cell panel and anti-tumor activity in an in vivo model of metastatic prostate cancer

Abstract # 4068

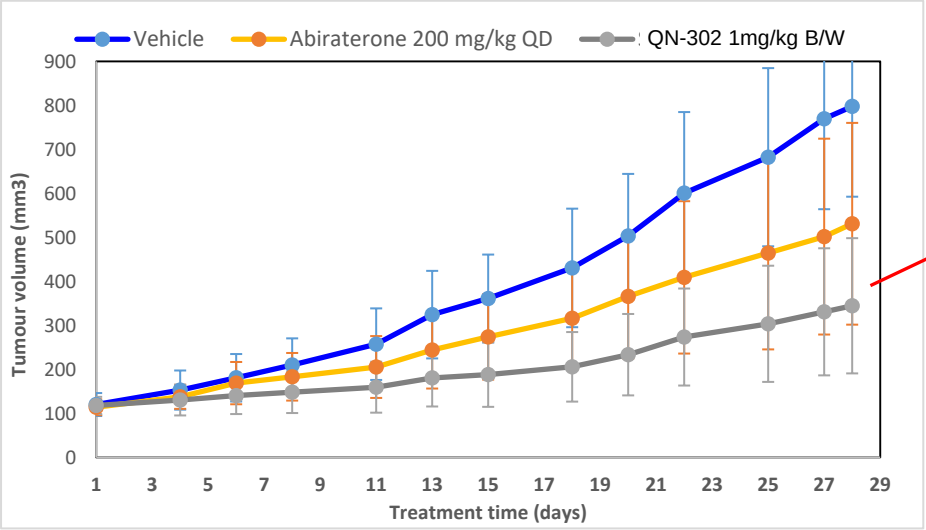
Nicole Williams[1] Jenny Worthington[1], Stephen Neidle[2]* and Ahmed Ahmed[2]

[1]*AXIS Bioservices, Coleraine, Northern Ireland BT51 3RP*
[2]*The School of Pharmacy, University College London, London WC1N 1AX, UK: s.neidle@ucl.ac.uk*

The compound QN-302, a tetra-substituted naphthalene diimide (ND) derivative has been designed to target quadruplex promoter sequences in cancer genes. It has low nM anti-proliferative activity in a panel of human cancer cell lines (Ahmed *et al*., *ACS Med Chem Lett*, 2020, **11**, 1634-1644) and has significant anti-tumor activity in several models for pancreatic cancer. We have also previously shown that two early-generation ND derivatives are active in both androgen-positive and negative prostate cancer cell lines (Mitchell *et al*, *Biochemistry*, 2013, **32**, 1429-1436) and that these down-regulate the transcription of quadruplex-containing genes.

We now report that QN-302 also shows significant anti-proliferative activity in a prostate cancer cell line panel, notably with an IC_{50} value of 3 nM in the PC3 cell line. Abiraterone has an IC_{50} in this line of 4820 nM. The PC3 line is derived from a metastatic carcinoma following androgen suppression therapy and is thus androgen independent and a model for castration-resistant prostate cancer when hormone therapies are no longer effective.

Encouraged by this level of activity and by favorable pharmacokinetic properties we have evaluated the activity of QN-302 in the PC3 xenograft model (in PBS solution, twice-weekly 1 mg/kg dose regimen IV administered), against a saline control and abiraterone, at a daily dose of 200 mg/kg PO administered, both over a 28-day period. QN-302 was well-tolerated, with no weight loss or other adverse effects in treated animals. QN-302 produced statistically highly significant anti-tumor activity relative to the controls. Abiraterone treatment also showed activity, albeit at a reduced level.



Prostate cancer lines	CM03	QN-302	Abiraterone	Enzalutamide
PC-3	94	3	4820	5350
DU145	113	32	N/A	N/A
LNCaP	394	247	3860	4820
VCaP	135	68	N/A	N/A
22RV1	90	90	N/A	N/A

Compounds were evaluated in a XTT (Roche) proliferation assay using the panel of cell lines shown in the table above. Calculated IC_{50} values are given in nM.

CM03 is an earlier generation ND compound with ca 10-fold lower activity than QN-302 in pancreatic cancer cell lines.

The *in vivo* study with the PC-3 prostate cancer xenograft model shows that QN-302 has statistically significant (p= 0.0008) anti-tumour activity in this model. Activity for abiraterone is at the p = 0.0382 level. T/C values on day 28 were 33.5% for QN-302 and 61.6% for abiraterone

QN-302 is bio-available at therapeutic doses and is well tolerated at these levels in this and other animal models of human cancers. It is currently in pre-clinical development with Qualigen Therapeutics Inc