Anti-cancer activity of the tumor-selective, hypoxia-inducing, agent BNC105 in platinum resistant ovarian cancer.

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Background

Ovarian cancer is a common cause of cancer mortality in women with limited treatment effectiveness in advanced stages. Despite modest improvements in patient outcomes as a result of surgery or platinum based chemotherapy, the majority of ovarian cancer patients relapse and die of their disease. There is a clear unmet medical need for more effective systemic therapy. BNC105 is a small molecule that exerts anti-cancer activity through disruption of tubulin polymerization (*Kremmidiotis et al, 2010; Flynn et al, 2011*). BNC105 causes selective occlusion of tumor blood vessels resulting in hypoxia and cancer cell necrosis. Furthermore, BNC105 exhibits direct cytotoxic activity against cancer cell lines in vitro. BNC105P is a phosphorylated prodrug form, which rapidly converts to the active agent BNC105 *in vivo.* A first in human Phase I clinical trial demonstrated that BNC105P has a favorable safety profile at the recommended dose of 16mg/m^2 and is associated with pharmacodynamic changes consistent with its known mechanism of action (*Rischin et al, 2011)*. BNC105P is currently under evaluation in a Phase I/II clinical trial for metastatic renal cell carcinoma in combination with the mTOR inhibitor Everolimus. With the aim of expanding the development of BNC105 in the clinic, we investigated its activity in preclinical models of ovarian cancer.

Methods & Results

Inhibition of human ovarian cancer cell line proliferation. The activity of BNC105 on the human ovarian carcinoma cell line A2780 and a derived cisplatin-resistant sub-line, A2780cis, was investigated using in vitro proliferation assays. BNC105 was a potent inhibitor of proliferation in both the A2780 and A2780cis cell lines with an EC50 of 0.25 nM and 0.13 nM respectively.

Compound	A2780 *EC50 (nM)*	A2780cis *EC50 (nM)*
BNC105	0.25	0.13
Cisplatin	312	4231
Carboplatin	9795	83621

Table 1. Inhibition of proliferation observed during in vitro exposure of the human ovarian cancer cell lines A2780 and A2780cis to BNC105, Cisplatin and Carboplatin.

Cisplatin and Carboplatin were considerably less potent than BNC105 against A2780 with EC50 values of 312 nM and 9795 nM respectively. Both Cisplatin and Carboplatin exhibited very low activity against the sub-line A2780cis (EC50 >4 uM) (**Table 1**).

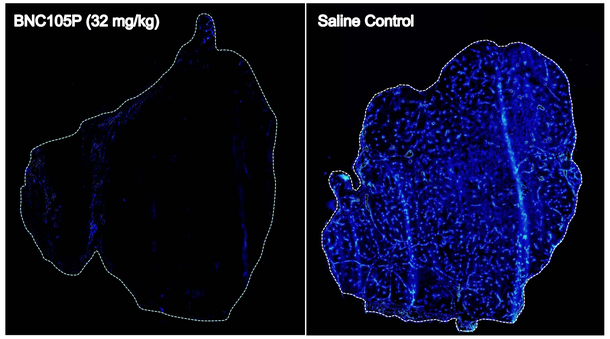

Figure 1. Inhibition of blood perfusion in A2780cis tumors following a single dose treatment of BNC105P (32mg/kg).

Disruption of blood flow in platinum resistant solid tumors following treatment with BNC105P. BALB/c-Foxn 1^{nu}/Arc mice bearing subcutaneous A2780cis solid tumors were treated with a single dose of BNC105P. Four hours post-treatment, animals were injected with H33342 and euthanized. Staining of tumor sections with H33342 was used as a measure of blood perfusion (*Kremmidiotis et al, 2010*). Tumors in mice treated with BNC105P exhibited very low staining with H33342. In contrast, tumors obtained from animals treated with the vehicle control displayed dense blood perfusion throughout (**Figure 1**).

BNC105P effectively suppresses the growth of platinum resistant tumors. Mice bearing A2780cis solid tumors were treated with two weekly doses of BNC105P at 32mg/kg. For comparison purposes, separate animal groups bearing A2780cis tumors were treated with either Cisplatin at 4mg/kg or Carboplatin at 80mg/kg. Consistent with the lack of activity exhibited by platinum agents for these cells in vitro, there was no therapeutic benefit seen in animals treated with either platinum agent. In contrast, BNC105P treatment resulted in a robust inhibition of tumor growth (**Figure 2**).

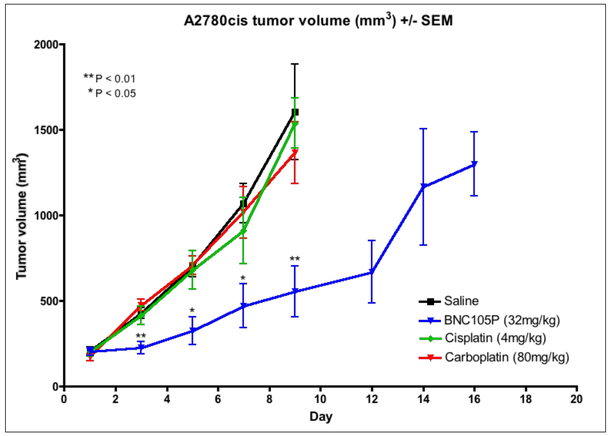

Figure 2. Tumor growth inhibition following treatment with BNC105P, Carboplatin or Cisplatin. Groups of BALB/c-Foxn 1^{nu}/Arc mice bearing A2780cis solid tumors were treated with BNC105P (32 mg/kg) on Day 1 and Day 8, Carboplatin (80mg/kg) Day 1 or Cisplatin (4mg/kg) on Day 1. Vehicle was administered on Days 1 and 8.

BNC105P confers a survival benefit in mice bearing A2780cis solid tumors. BALB/c-Foxn 1^{nu}/Arc mice bearing A2780cis tumors were treated with BNC105P, Cisplatin or Carboplatin. All animals receiving the platinum based treatments reached ethical the termination endpoint by Day 10 (**Figure 3**). Animals treated with BNC105P survived longer, reaching the ethical termination endpoint at Day 28.

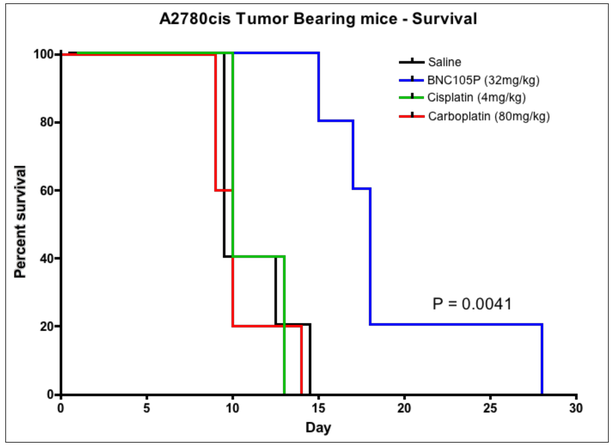

Figure 3. Animal survival following treatment with BNC105P, Carboplatin or Cisplatin. Groups of BALB/c-Foxn 1^{nu}/Arc mice bearing A2780cis solid tumors were treated with BNC105P (32 mg/kg) on Day 1 and Day 8, Carboplatin (80mg/kg) Day 1 or Cisplatin (4mg/kg) on Day 1. Vehicle was administered on Days 1 and 8.

Conclusion

BNC105 is very effective in inhibiting the proliferation of the human ovarian cancer cell lines A2780 and A2780cis at sub 1nM concentrations.

BNC105P treatment inhibits tumor blood perfusion, suppresses the growth of solid tumors arising from the platinum resistant cell line A2780cis and improves animal survival.

It is reasonable to hypothesize that BNC105 has therapeutic application in this cancer setting. Clinical evaluation of BNC105 in ovarian cancer is warranted.

References

1. Kremmidiotis et al. Mol Cancer Ther. 2010 Jun;9(6):1562-73.
2. Flynn et al. J Med Chem. 2011 Sep 8;54(17):6014-27.
3. Rischin et al. Clin Cancer Res. 2011 Aug 1;17(15):5152-60.