Anti-cancer activity of the tumor-selective, hypoxia-inducing, agent BNC105 in platinum resistant ovarian cancer.
Tina C. Lavranos, Annabella F. Leske, Daniel J. Inglis, Chloe K. Brown, David C. Bibby and Gabriel Kremmidiotis

Abstract # 2774

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/m2 and is associated with pharmacodynamic changes consistent with its known activity in vitro. Kremmidiotis et al, 2010; Flynn et al, 2011).

Methods & Results

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).

Table 1
<table>
<thead>
<tr>
<th>Compound</th>
<th>EC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNC105</td>
<td>0.25</td>
</tr>
<tr>
<td>A2780cis</td>
<td>0.13</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>312</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>9795</td>
</tr>
</tbody>
</table>

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 1nu/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).

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

BNC105 confers a survival benefit in mice bearing A2780cis solid tumors. BALB/c-Foxn 1nu/Arc mice bearing A2780cis solid tumors were treated with BNC105P or Cisplatin. 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.

References