Identification of plasma biomarker concentration changes resulting from the administration of the Vascular Disrupting Agent BNC105 across 3 clinical trials in mesothelioma, ovarian and renal cancer

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Abstract No. 1551
AARC 2015

Biomarkers Associated with BNC105 Treatment

**RESULTS**

With the aim of identifying pharmacodynamic biomarkers associated with BNC105 treatment we measured changes in plasma concentrations for a panel of plasma analytes across three clinical trials, where BNC105 was utilized as a monotherapy or in combination with other established anticancer agents. We analyzed 'change in plasma concentration for each analyte by comparing plasma levels before and after administration of BNC105 in each patient. Overall, gemcitabine/carboplatin treatment amplified BNC105-induced changes in plasma analytes. A greater number of analytes increased with BNC105 patients treated concomitantly with gemcitabine/carboplatin with the amplitude of increase being considerably higher than that seen in the mesothelioma trial where BNC105 was used as a monotherapy. The amplitude of plasma analyte changes was lowest in the renal cancer trial where BNC105 was combined with everolimus. Of the panel of analytes investigated, 5 displayed overall increased plasma concentration following treatment with BNC105 in all 3 clinical trials. These analytes were Ferritin, IL-6, IL-10, MCP-1 and SFRP-1. MMP9 and TIMP2 were not evaluated in the mesothelioma trial but displayed plasma concentration changes following BNC105 administration in both the ovarian and the renal cancer trials.

**METHODOLOGY**

**INTRODUCTION**

BNC105 is a tubulin-depolymerisation agent. Its activity includes effects on both cancer cells and on solid tumor microcirculation. BNC105 shows evidence of strong anti-cancer efficacy in vitro and in animal models. In solid tumor its efficacy is driven by selective destruction of tumor vessels (Vascular Disrupting Agent - VDA) and direct action on tumor cells through suppression of their proliferation. In non-proliferating blood cancers (e.g. Chronic Lymphocytic Leukemia) BNC105 activates pro-apoptotic proteins, which mediates cancer cell death. BNC105 may be used in the treatment of human cancers both as a monotherapy and also in combination therapies. To date BNC105 has been evaluated in mesothelioma as a monotherapy, in ovarian cancer in combination with gemcitabine/carboplatin and in renal cancer in combination with everolimus. Seventy four (74) patients receiving intravenous administrations of BNC105 in these trials were blood sampled at baseline and following BNC105 administration. The plasma concentrations of a panel of 83 plasma analytes were investigated for changes resulting from the administration of BNC105. Here, we report data across the three clinical trials on plasma biomarkers that change in response to the administration of BNC105. Association of these biomarker changes with clinical benefit is shown for the phase II clinical trial in renal cancer patients.

Blood drawn for biomarker assessments in each trial were pre-specified and optimal. Patients receiving BNC105 alone or in combination with other agents received blood draw immediately prior to BNC105 administration and 1 to 3 hours following BNC105 administration. Plasma samples were used to determine plasma concentrations for a combined list of 83 exploratory plasma analytes using Multianalyte Protein (MAP) technology (BioData MBM).

Determine 'change from baseline for each biomarker in each patient'

Use median of 'change from distribution for each biomarker to categorize patients in 2 groups

<table>
<thead>
<tr>
<th>Indication</th>
<th>Phase</th>
<th>Treatment</th>
<th>Number of patients sampled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian Cancer I</td>
<td>I</td>
<td>Gemcitabine (800-1000mg/m2); Carboplatin (AUC 4)</td>
<td>11</td>
</tr>
<tr>
<td>Renal Cancer II</td>
<td>II</td>
<td>Gemcitabine (1400mg/m2)*; BNC105 (12-16mg/m2)</td>
<td>44</td>
</tr>
<tr>
<td>Ovarian Cancer II</td>
<td>II</td>
<td>Carboplatin (AUC 4); BNC105 (12-16mg/m2)</td>
<td>25</td>
</tr>
<tr>
<td>Renal Cancer I</td>
<td>I</td>
<td>BNC105 (12-16mg/m2)*</td>
<td>19</td>
</tr>
</tbody>
</table>

Blood samples were obtained at baseline and post-administration of BNC105. Each patient evaluated is presented as a dot. Percent change for each biomarker was calculated as follows:

\[
\text{Percent change} = \frac{\text{post} - \text{baseline}}{\text{baseline}} \times 100
\]

**RESULTS**

**Correlation of Biomarker Changes with Clinical Benefit in the Renal Cancer Trial**

**CONCLUSIONS**

- Ferritin, IL-6, IL-16, MCP-1, MMP9 and TIMP2 displayed increased plasma levels in patients receiving treatment with the Vascular Disrupting Agent (VDA) BNC105 across different clinical trials. These may represent good biomarkers of pharmacodynamic response to VDA action.
  - We have previously shown that Ferritin and IL-8 plasma levels at baseline correlate with PFS, with 98% of patients having high levels of Ferritin and low levels of IL-8 experiencing PFS>6 months (Abstract #475, ASCO GU, 2015).

  - MMP9, SCF, SHBG and SAP plasma concentration changes following BNC105 treatment correlate with PFS in renal cancer patients treated with BNC105/everolimus and can be used to enrich for patients that experience longer PFS.

  - Further exploration of these biomarkers in subsequent clinical trials with BNC105 is warranted.