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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INTRODUCTION

BNC105 is a tubulin depolymerisation agent. Its activity includes effects on both cancer cells and on solid tumor microvasculature. BNC105 shows evidence of strong anti-cancer efficacy *in vitro* and in animal models. In solid tumors its efficacy is driven by selective destruction of tumor vasculature (Vascular Disrupting Agent – VDA) and direct action on tumor cells through suppression of their proliferation. In non-proliferating blood cancers (e.g. Chronic Lymphocytic Leukaemia) BNC105 activates pro-apoptotic proteins, which mediate cancer cell death. BNC105 may be useful 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.

METHODOLOGY

Indication	Phase	Treatment	Number of patients sampled
Mesothelioma	II	BNC105 (16mg/m^2)*	19
Ovarian Cancer	I	Gemcitabine (800-1000mg/m^2); Carboplatin (AUC 4) BNC105 (12-16mg/m^2)*	11
Renal Cancer	II	Everolimus(10mg) BNC105 (16mg/m^2)*	44

**BNC105 was administered in its pro-drug form BNC105P (Rischin et al, 2011 Clin Cancer Res17:5152*

Table 1. Clinical trials included in the biomarker analyses presented in this poster. Cancer indication, treatment and number of patients included in the biomarker analysis are shown.

Blood draws for biomarker assessments in each trial were pre-specified and optional. Patients receiving BNC105 alone or in combination with other agents received blood draws immediately prior to BNC105 administration and 1 to 3 hours following BNC105 administration. Plasma samples were used to determine plasma concentrations for a combined total of 83 exploratory plasma analytes using Multi-Analyte Profile (MAP) technology (Myriad RBM®).

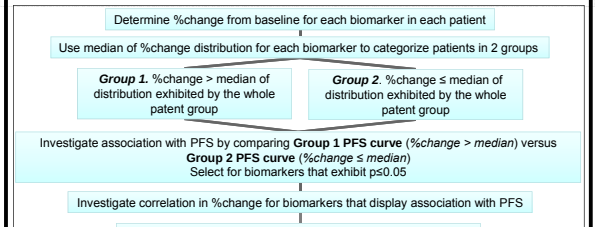

Figure 1. Flow chart illustrating the analyses employed to identify biomarkers associated with clinical benefit (Progression Free Survival (PFS)) in the renal cancer clinical trial.

A total of 42 analytes displayed concentrations below the lower limit of quantification and were not considered further. For the renal cancer trial median values for each biomarker (expressed as %change in plasma concentration, Figure 2) were used as a reference point for stratification of patients into two groups which were then evaluated for correlation with the efficacy endpoint of 6 month PFS (Figure 1) (*Keyvanhar et al. 2012 J Translational Medicine 10:165*). Time-to-event analysis was performed using Kaplan-Meier curves and results compared using log-rank test.

RESULTS

Biomarkers Associated with BNC105 Treatment

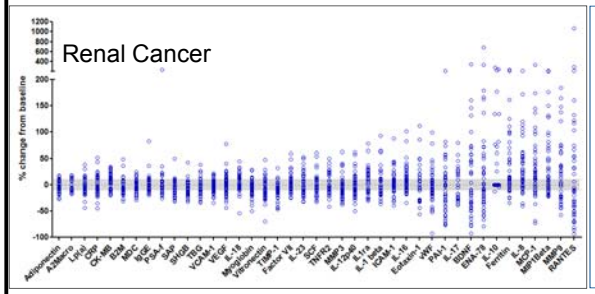

Figure 2. Graph showing %change from baseline for each biomarker evaluated in the renal cancer clinical trial. Each patient evaluated is presented as a dot. Percent change for each biomarker was calculated as follows:

$$\frac{C_{post} - C_{baseline}}{C_{baseline}} \times 100$$

C_{post}= analyte plasma concentration following administration of BNC105
$C_{baseline}$= analyte plasma concentration prior to administration of BNC105

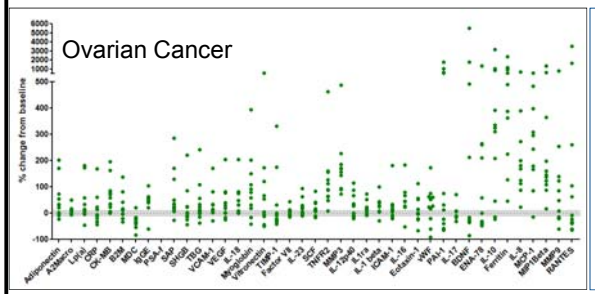

Figure 3. Graph showing %change from baseline for each biomarker evaluated in the ovarian cancer clinical trial. Each patient evaluated is presented as a dot. Percent change for each biomarker was calculated as follows:

$$\frac{C_{post} - C_{baseline}}{C_{baseline}} \times 100$$

C_{post}= analyte plasma concentration following administration of BNC105
$C_{baseline}$= analyte plasma concentration prior to administration of BNC105

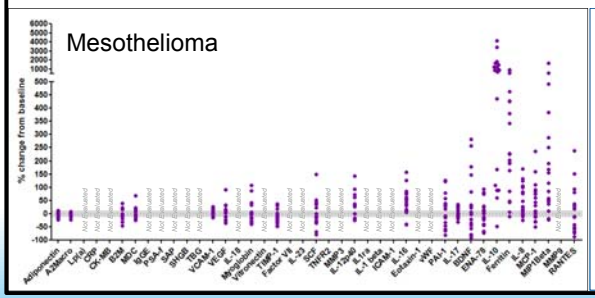

Figure 4. Graph showing %change from baseline for each biomarker evaluated in the mesothelioma clinical trial. Each patient evaluated is presented as a dot. Percent change for each biomarker was calculated as follows:

$$\frac{C_{post} - C_{baseline}}{C_{baseline}} \times 100$$

C_{post}= analyte plasma concentration following administration of BNC105
$C_{baseline}$= analyte plasma concentration prior to administration of BNC105

With the aim of identifying pharmacodynamic biomarkers associated with BNC105 treatment we measured changes in plasma concentration for a panel of plasma analytes across three clinical trials, where BNC105 was utilised as a monotherapy or in combination with either everolimus or carboplatin/gemcitabine. Our analyses determined %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 in 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-8, IL-16, MCP-1 and MIP-1β. MMP9 and TNFR2 were not evaluated in the mesothelioma trial but displayed plasma concentration changes following BNC105 administration in both the ovarian and the renal cancer trials.

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

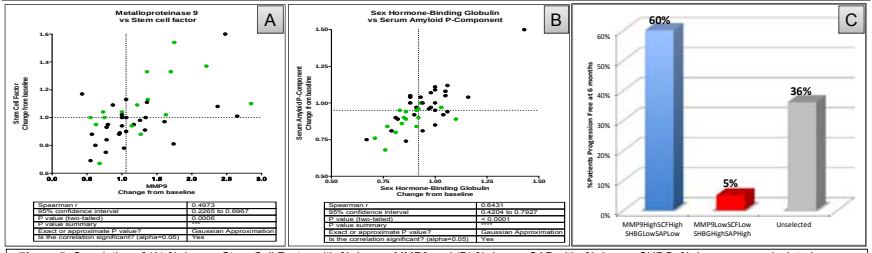

Figure 5. Correlation of (A) %change Stem Cell Factor with %change MMP9 and (B) %change SAP with %change SHBG. %change was calculated as shown in Figure 2. The value for each patient is represented with a dot. Patients with PFS<6 months are represented by black dots, patients with PFS>6 months are represented by green dots. (C) Percent of patients with PFS>6 months in relation to biomarker groupings. Percent of patients with PFS>6 months for the unselected patient population is also shown.

Given the larger number of patients enrolled in the phase II renal cancer trial, we sought to identify potential biomarker combination signatures that may be associated with better outcomes for patients receiving BNC105 in combination with everolimus. Based on the %change data shown in Figure 2, the analytes in our panel can be distinguished into 3 main categories: i) there was an overall increase in the plasma concentration following administration of BNC105 (e.g. Ferritin, IL8, MCP-1); ii) there was an overall decrease in the plasma concentration following administration of BNC105 (e.g.TIMP-1, SAP); and 3) the concentration was increased in some patients but decreased in others (e.g. RANTES, BDNF). We used the median value of the patient distribution for each biomarker to stratify patients in 2 groups for each analyte and subsequently correlate with PFS as described in Figure 1. Our analysis showed that 4/41 analytes investigated displayed a statistically significant correlation with PFS (*Pal et al, 2015, Clin Cancer Res, in press*). Increased concentration of MMP9 and SCF following BNC105 treatment was associated with better PFS (MMP9 (p=0.0421); SCF (p=0.0291)). Decreased concentration of SHBG and SAP following BNC105 treatment was associated with better PFS (SHBG (p=0.0063); SAP (p=0.0184)). Interestingly, %change for MMP9 correlates well with %change SCF and similarly %change for SHBG correlates well with %change SAP (Figure 5A, 5B). Delineation of patients based on these 4 biomarkers enables enrichment for patients that experienced PFS>6 months on the BNC105+everolimus treatment (Figure 5C).

CONCLUSIONS

- **Ferritin, IL8, IL16, MCP-1, MIP-1b, MMP9 and TNFR2 displayed increased plasma levels in patients receiving treatment with the Vascular Disruption 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 IL8 plasma levels at baseline correlate with PFS, with 98% of patients having high levels of Ferritin and low levels of IL8 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.**