A Phase I/II trial of BNC105P with everolimus in metastatic renal cell carcinoma (mRCC) patients: Updated Phase I results of the DisrupTOR-1 trial (Hoosier Oncology Group)

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Background

- BNC105 is a small molecule that selectively disrupts tumor vasculature causing hypoxia that leads to tumor necrosis (Kremmidiotis *et al*, 2010). BNC105 achieves its pharmacological effects through disruption of tubulin dynamics resulting in endothelial cell morphological changes and tumor blood vessel occlusion.
- BNC105P is a disodium formulation that enables *i.v.* administration and readily converts to the active drug BNC105 upon administration.
- Preclinical evaluation of BNC105 activity in renal cancer models has demonstrated that despite the high degree of hypoxia and necrosis caused by BNC105 several proteins are activated/upregulated by a small surviving cancer cell population that leads to tumor recovery. These molecules include VEGF, HIF-1, PERK and mTOR.
- We reasoned that concurrent induction of hypoxia by BNC105 and inhibition of mTOR by everolimus would prevent tumor recovery and maximise the impact of BNC105 induced tumor necrosis yielding higher therapeutic benefit.

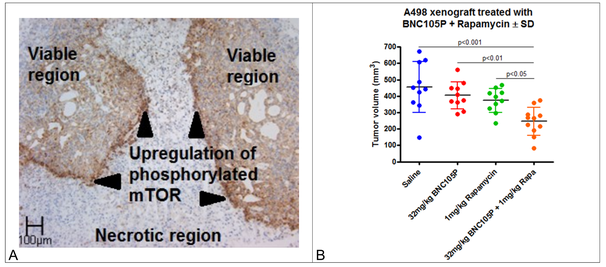

Figure 1. Mice bearing A498 renal cell line tumors were treated with BNC105 alone or in combination with the mTOR inhibitor rapamycin. **(A)** BNC105 causes tumor necrosis. Small subpopulation of surviving cancer cells upregulate mTOR phosphorylation. **(B)** BNC105 combined with mTOR inhibition increases tumor growth suppression.

Methods

Study Objectives

Phase I

Primary
To determine maximum tolerated dose (MTD) and toxicities of BNC105P in combination with everolimus.

Secondary
To determine the response rate of BNC105P in combination with everolimus.
To evaluate the pharmacokinetic (PK) profile for BNC105P in combination with everolimus.

Phase II

Primary
Improvement in 6-month Progression-Free Survival (PFS) with the addition of BNC105P to everolimus.

Secondary
To determine response rate and overall survival (max. 5 years) with combination therapy compared to everolimus alone.
To determine PFS with BNC105P alone in patients progressing on everolimus.
To evaluate the adverse events of the combination.

Exploratory Objective
To determine the correlation of PFS with biomarkers.

Key Eligibility Criteria

1. Histological or cytological proof of component (any percent) of clear cell RCC (renal cell carcinoma). No component of collecting duct or medullary histology is permitted. Up to 30% sarcomatoid histology is acceptable.
2. Metastatic or locally advanced unresectable RCC (prior nephrectomy is not mandatory).
3. Progressive disease after 1-2 prior VEGF-directed tyrosine kinase inhibitors (TKIs).
4. Measurable disease according to RECIST. No active brain metastases.
5. No prior treatment with temsirolimus or everolimus in the Phase II component.
6. Corrected QT interval (QTc) ≤450 msec.
7. No uncontrolled hypertension, BP >150/100mmHg despite use of anti-hypertensive medication(s).
8. No thrombotic event and no significant cardiovascular events within 6 months of registration.
9. No history of clinical CHF or LVEF <50% by Echo (or MUGA) within 30 days of registration.

Study Design

Phase I (combination)
4 dose levels of BNC105P, 3+3 design, N=12

BNC105P: 4.2 mg/m^2
Everolimus: 10 mg oral, daily

BNC105P: 8.4 mg/m^2
Everolimus: 10 mg oral, daily

BNC105P: 12.6 mg/m^2
Everolimus: 10 mg oral, daily

BNC105P: 16 mg/m^2
Everolimus: 10 mg oral, daily

Phase II (combination vs. sequential regimen)
#N=61 per arm

RANDOMIZE

Arm A: Combination
BNC105P:
at phase I MTD
Everolimus:
10 mg oral, daily

Arm B: Sequential
Everolimus:
10 mg oral, daily

Progressive disease *
Continue therapy until progressive disease or unacceptable toxicity.

BNC105P:
16 mg/m^2

Continue therapy until progressive disease or unacceptable toxicity
(max. of 12 cycles)

Figure 2. Schema of protocol # GU09-145.

#Phase II Statistical Consideration
Powered to detect an improvement in 6-month PFS from 36% with everolimus to 60% with the combination. Patients will be stratified for MSKCC risk group (good, intermediate, poor) and number of prior TKIs (1 vs. >1). Group sample sizes of 61 per group achieve 80% power, using a one-sided Chi-square test with continuity correction and with a significance level of 0.05. Assuming that ~ 10% of patients may be inevaluable, a total of 122 + 10%, i.e. 134 patients will be enrolled in the Phase II.

Drug Administration
BNC105P: administered by IV injection over 10 minutes on Day 1 & Day 8 every 21 days.
Everolimus: orally administered (10 mg) daily; 7 day lead in prior to administration of BNC105P.

Study Assessments

Radiological Assessments
- Assessment of tumors with a CT scan of the chest, abdomen and pelvis after every 3 cycles (~ 9 weeks).
- Echo (or MUGA) every 4 cycles
- Bone scan every 3 cycles, if performed at baseline and if clinically indicated.

Other Assessments
- Physical examination, including vital signs and body weight
- Karnofsky Performance Status
- Adverse Events
- Concomitant Medication
- ECG
- CBC; Complete metabolic profile; LDH; Lipid panel; Urinalysis

Correlatives
- Phase I: PK whole blood and plasma samples in Cycle 1
  Optional serum and plasma for biomarker analysis in Cycle 1
- Phase II: Optional serum and plasma for biomarker analysis in Cycle 1
  Optional unstained tissue slides from previous renal biopsy

Results

Phase I Dosing & Safety Data

- The previously identified MTD of BNC105P (16 mg/m^2) can be combined with full dose everolimus (10 mg p.o.).
- No Dose Limiting Toxicities (DLTs) and no evidence of cumulative toxicities following treatment duration of up to 18 months.
- Eight of the twelve Phase I patients achieved disease stabilization.
- Median treatment period across the eight patients with stable disease was 11 cycles (range 5-24).

Dose level of BNC105P (mg/m^2) + Everolimus 10 mg p.o.	Assigned Patient No.	Cycles Completed	Best Response*	Adverse event related to Everolimus or BNC105P or combination** (≥ Grade 2)
4.2	01	12	SD	G2 dyspepsia, G2 hemoglobin, G2 cough
	02	3	PD	G2 AST-SGOT
	03	1	PD	
8.4	04	15	SD	G2 low platelets
	05	3	PD	G2 weight loss, G2 hypomagnesemia, G3 hemoglobin
	09	10	SD	
12.6	12	5	SD	G2 fatigue
	13	12	SD	G2 nail infection, G2 hemoglobin, G2 left ventricular systolic dysfunction
	14	24	SD	G2 hemoglobin, G2 mucositis (oral)
16	15	6	SD	G2 diaphoresis, G2 hemoglobin, G3 pericardial effusion, G2 pleural effusion
	16	3	PD	G2 mucositis (oral), G2 fatigue
	17	5	SD	

*Interim data (February 2013) **Deemed at least possibly-related to either or both study drugs

Table 1. Interim data in Phase I patients: Doses administered, RECIST response and Adverse Events

Phase I Biomarker Analysis

ANALYTES ABOVE LLQ		ANALYTES BELOW LLQ	
Adiponectin	Interleukin-23 (IL-23)	Amphiregulin (AR)	Interleukin-15 (IL-15)
α-2-Macroglobulin (A2Macro)	Kallikrein-7 (KLK-7)	Betacellulin (BTC)	Interleukin-17 (IL-17)
β-2-Microglobulin (B2M)	Macrophage-Derived Chemokine (MDC)	Epidermal Growth Factor (EGF)	Macrophage Inflammatory Protein-1α (MIP-1α)
Brain-Derived Neurotrophic Factor (BDNF)	Macrophage Inflammatory Protein-1β (MIP-1β)	Epiregulin (EPR)	Maspin
Collagen IV	Matrix Metalloproteinase-3 (MMP-3)	Fibroblast Growth Factor basic (FGF-basic)	Placenta Growth Factor (PLGF)
Creatine Kinase-MB (CK-MB)	Matrix Metalloproteinase-9 (MMP-9)	Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)	Platelet-Derived Growth Factor-BB (PDGF-BB)
Eotaxin-1	Mesothelin (MSLN)	Heparin-Binding EGF-Like Growth Factor (HB-EGF)	Prostate-Specific Antigen, Free (PSA-f)
Epidermal Growth Factor Receptor (EGFR)	Monocyte Chemotactic Protein-1 (MCP-1)	Immunoglobulin E (IgE)	Transforming Growth Factor α (TGFα)
Epithelial-Derived Neutrophil-Activating Protein 78 (ENA-78)	Myoglobin	Interferon-γ (IFN-γ)	Tumor Necrosis Factor α (TNFα)
Factor VII	Plasminogen Activator Inhibitor-1 (PAI-1)	Interleukin-1α (IL-1α)	Tumor Necrosis Factor β (TNFβ)
Ferritin (FRTN)	Prostasin	Interleukin–1β (IL-1β)	Vascular Endothelial Growth Factor-B (VEGF-B)
HE4	Stem Cell Factor (SCF)	Interleukin-2 (IL-2)	
Hepatocyte Growth Factor Receptor (HGFR)	T Cell-Specific Protein RANTES	Interleukin-3 (IL-3)	
Intercellular Adhesion Molecule 1 (ICAM-1)	Tenascin-C (TN-C)	Interleukin-4 (IL-4)	
Interleukin-1 receptor antagonist (IL-1ra)	Tissue Inhibitor of Metalloproteinases-1 (TIMP-1)	Interleukin-5 (IL-5)	
Interleukin-8 (IL-8)	Tumor Necrosis Factor receptor-2 (TNFR2)	Interleukin-6 (IL-6)	
Interleukin-12 (IL-12)	Vascular Cell Adhesion Molecule-1 (VCAM-1)	Interluekin-7 (IL-7)	
Interleukin-12 Subunit p40 (IL-12p40)	Vascular Endothelial Growth Factor-C (VEGF-C)	Interleukin-10 (IL-10)	
Interleukin-16 (IL-16)	Vascular Endothelial Growth Factor (VEGF)	Interleukin-12 Subunit p70 (IL-12p70)	
Interleukin-18 (IL-18)	Vascular Endothelial Growth Factor-D (VEGF-D)	Interleukin-13 (IL-13)	

Table 2. List of serum/plasma analytes investigated prior to administration of BNC105P (baseline) and 3 hours following administration of BNC105P on C1D1 and C1D8. Values for a number of analytes were below the lower limit of quantification (LLQ).

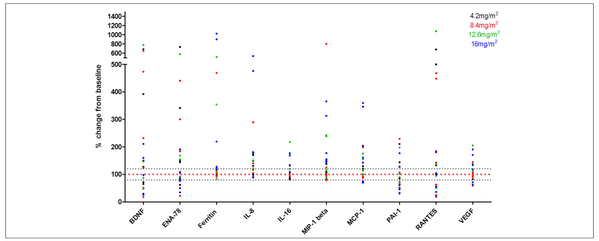

Figure 3. Serum/plasma analytes displaying notable changes from baseline following administration of BNC105P. Baseline measurements derived from C1D1 and C1D8 were averaged and compared to the average of the 3 hour measurements obtained from C1D1 and C1D8. Percent change from the baseline was calculated as follows:

$$\%change = (C1D1_{post\ 3hrs} + C1D8_{post\ 3hrs}/2)/(C1D1_{baseline} + C1D8_{baseline}/2) \times 100$$

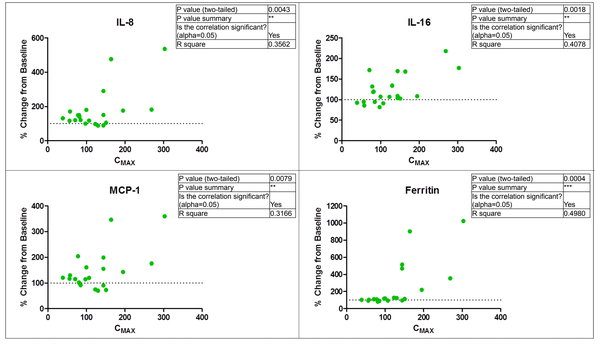

Figure 4. Serum/plasma analytes displaying changes from baseline following administration of BNC105P that correlated with BNC105 plasma levels (C_{MAX}). Each data point represents analyte change from baseline at either C1D1 or C1D8. Percent change was calculated as follows:

$$\%change = (C1D1_{post\ 3hrs}/C1D1_{baseline}) \times 100$$
$$\%change = (C1D8_{post\ 3hrs}/C1D8_{baseline}) \times 100$$

Conclusions

- PK analysis in the Phase I patients indicates no drug-drug interaction between BNC105P and everolimus.
- The combination of everolimus and BNC105P is well tolerated with no dose limiting toxicities in the Phase I patients or evidence of cumulative toxicity.
- Eight of the twelve Phase I patients achieved disease stabilization. Median treatment period across the eight patients with stable disease was 11 cycles (range 5-24).
- Changes in biomarkers associated with vascular response suggest that BNC105 reaches plasma levels of pharmacological significance. Changes in these biomarkers will be correlated with PFS in the Phase II.

Reference

Kremmidiotis *et al*. Molecular Cancer Therapeutics, 9 June 2010.

Trial registration number: NCT01034631