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Phase I results of a phase I/II trial of BNC105P with everolimus in metastatic renal cell carcinoma (mRCC) patients previously treated with VEGFR tyrosine kinase inhibitors. (Hoosier Oncology Group)

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Background

BNC105 :

BNC105 is a small molecule that acts as an inhibitor of tubulin polymerization.

BNC105P is a phosphorylated prodrug form which rapidly converts to the active agent BNC105 *in vivo*.

The pharmacological effect seen with BNC105 is mediated through selective damage of tumor endothelial cells, leading to an occlusion of blood flow to the tumor and subsequent tumor necrosis (i.e. BNC105 acts as a vascular disruption agent, VDA).

BNC105 also has a direct anti-proliferative action of cancer cells. (Kremmidiotis *et al.* 2010).

BNC105 / mTOR Inhibitor Combination :

RCC is an angiogenesis-dependent and hypoxia-driven malignancy and the significance of the mTOR signaling pathway in this tumor type is well recognized.

In addition, tumor hypoxia (following vascular disruption) results in the activation of hypoxia inducible factor 1α (HIF-1α) and increased expression of genes involved in angiogenesis such as VEGF and the PI3K/Akt/mTOR pathway (Ellis et al. 2012).

The up regulation of the PI3K/Akt/mTOR pathway is a 'survival' response by the tumor to hypoxic insult. This has been demonstrated in a Caki-1 (VHL wild type) cell line xenograft model in mice administered BNC105P (Fig. 1).

The combined use of this VDA with an agent active against mTOR may improve clinical outcome. A phase I/II study of a regimen consisting of everolimus (mTOR inhibitor) and BNC105P (VDA) is underway in renal cell carcinoma.

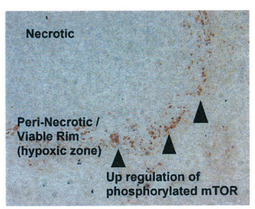


Fig. 1: Evaluation of phosphorylated mTOR in a Caki-1 (VHL wild type) xenograft treated with BNC105P (mouse model).

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 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.
To determine the overall survival, up to a maximum of 5 years.

Exploratory Objective
To determine the correlation of PFS with biomarkers.

Trial registration number: NCT01034631 (clinicaltrials.gov)

Key Eligibility Criteria

Histological or cytological proof of component (any percent) of clear cell RCC (renal cell carcinoma). No component of collecting duct, medullary histology is permitted. Up to 30% sarcomatoid histology is acceptable.
Metastatic or locally advanced unresectable RCC. NOTE: Prior nephrectomy is not mandatory.
Progressive disease after 1-2 prior VEGF-directed tyrosine kinase inhibitors (TKIs).
Karnofsky Performance Score (KPS) ≥70.
Measurable disease according to RECIST. No active brain metastases. No other currently active malignancy.
No treatment with any other chemotherapy agent within 14 days prior to registration (30 days for bevacizumab). Prior radiation therapy to <25% of the bone marrow allowed if completed within 30 days prior to registration.
Corrected QT interval (QTc) ≤450 msec.
WBC >3.5 K/mm^3, hemoglobin >8.5 g/dL, platelets >100 K/mm^3, ANC >1.5 K/mm^3, serum creatinine <2.5 x ULN (upper limit normal), total bilirubin <1.25 x ULN, aminotransferase (AST, ALT) <2.5 x ULN, INR <1.5 x ULN.
No prior treatment with temsirolimus or everolimus in the phase II component.
No use of full dose, therapeutic anti-coagulation with warfarin or related anti-coagulants.
No uncontrolled hypertension, BP >150/100mmHg despite use of anti-hypertensive medication(s).
No thrombotic event and no significant cardiovascular events within 6 months of registration.
No history of clinical CHF or LVEF <50% by Echo (or MUGA) within 30 days.
No grade 2 or greater peripheral neuropathy.

Study Design

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

Administered until evidence of progressive disease or unacceptable toxicity.

PK assessment.

- **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)

Drug Administration

BNC105P: administered by IV injection over 10 min on Day 1 & Day 8 every 21 days.

Everolimus : orally administered (10 mg) daily; 7 day lead in prior to administration of BNC105P.

Fig 2: Schema of protocol # GU09-145.

Statistical Considerations

Phase I
3+3 design, 4 cohorts, N=12-24. MTD is defined at the dose where <33 % of the subjects experience a DLT (i.e. 0/3 or 1/6).

Randomized Phase II
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.
Safety analyses will be performed using the Intent-To-Treat population. A maximum of 5 years follow-up will be employed.

Study Assessments

Radiological Assessments
Assessment of tumors with a CT scan of the chest, abdomen, and pelvis will be performed after every 3 cycles (~ 9 weeks).
Echo (or MUGA) will be performed every 4 cycles, but earlier if warranted.
A bone scan will be repeated after every 3 cycles, if performed at baseline and if clinically indicated.

Other
Physical examination, including vital signs and body weight.
Karnofsky Performance Status.
Adverse Events.
Concomitant Medication.

Phase I: Mandatory PK whole blood and plasma samples collected on Cycle 1.
Phase II: Optional collection of serum and plasma for biomarker analysis on Cycle 1 during BNC105P treatment.

Optional unstained tissue slides from the patient's previous renal biopsy if available.
Complete Blood Count (CBC) with differential and platelet count.
Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen, total carbon dioxide, albumin, total bilirubin, alkaline phosphatase, AST, ALT), phosphorus and electrolytes.
LDH, Lipid Panel.

Results

Phase I Dosing & Safety Data

- First patient visit occurred in April 2010. Twelve patients were enrolled to the phase I component of the study and completed at least 1 cycle of the BNC105P/everolimus combination (Table 1).
- The combination was well tolerated with no drug-related, Dose Limiting Toxicities (DLT) being observed in any of the phase I patients.
- The previously identified MTD of BNC105P (16 mg/m^2) can be combined with full dose everolimus.
- There is no evidence of cumulative toxicities at this time.
- Several phase I patients achieved at least disease stabilization. Five patients received at least 10 cycles of the combination. Two patients remain on treatment as of May 2012.

Table 1: Doses administered and Adverse Events observed in phase I patients*.

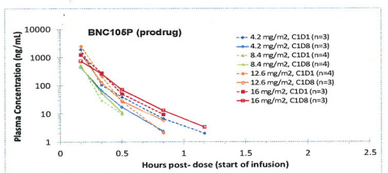
Dose level of BNC105P (mg/m^2) + Everolimus 10 mg p.o.	Cycles Completed	Remains on Study	Adverse event related to Everolimus or BNC105P or combination** (≥ Grade 2)
4.2	12		G2 dyspepsia, G2 hemoglobin, G2 cough
	3		G2 AST-SGOT
	1		
8.4	15		G2 low platelets
	3		G2 weight loss, G2 hypomagnesemia, G3 hemoglobin
	10		
12.6	5		G2 fatigue
	12		G2 nail infection, G2 hemoglobin
	14	Y	G2 hemoglobin, G2 mucositis (oral)
16	6		G2 diaphoresis, G2 hemoglobin
	3		G2 mucositis (oral), G2 fatigue
	5	Y	

* interim data (May 2012) ** deemed at least possibly-related

- The phase II component of the study commenced in September 2011 and is ongoing.
- More than 30 US-based sites have opened protocol GU09-145 at their institution.

Pharmacokinetics

- PK analysis was performed on plasma (BNC105P and BNC105) and whole blood (everolimus) samples collected from phase I patients (Fig. 3). Samples were collected at predose and up to 6 h following administration of BNC105P in Cycle 1 (Days 1 and 8).
- The PK of BNC105P and BNC105 correlated well with that previously reported by Rischin *et al.* 2011.
- BNC105P was rapidly converted to BNC105, with a mean half-life of 0.13 hours. The maximal plasma concentration of BNC105 occurred at the end of the infusion in all subjects. The elimination rate of BNC105 immediately post-dose appears to be first-order, with the rate becoming slower by 30 minutes post-dose. The mean half-life of BNC105 was 0.63 hours.
- There was no trend observed in the plasma levels of either BNC105P or BNC105 between the Day 1 and Day 8 profiles, indicating no change in metabolism between Days 1 and 8.
- Everolimus was administered concurrently (10 mg p.o. each evening) with BNC105P. In addition, a 7 day lead-in dose of everolimus was administered prior to the first administration of BNC105P. Thus, everolimus was near/at steady state prior to the administration of BNC105P. The mean concentration of everolimus in blood was 17.8 ng/mL (across all subjects, sample times = 0 to 6 h post **administration of the BNC105P) and correlated well with levels previously reported by O'Donnell** *et al.* 2008.
- No evidence of a drug interaction between BNC105P and everolimus was observed.



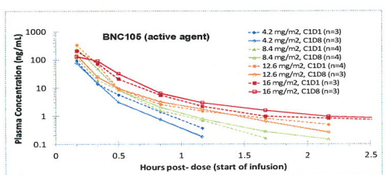


Fig 3: Mean plasma concentration of BNC105P and BNC105 by dose level (mg/m^2) and study day (Cycle 1 Day 1 & 8)

Conclusions

- Everolimus and BNC105P can be combined at their full doses. Everolimus (10 mg p.o.) is well tolerated when combined with the previously identified RP2D of BNC105P (16 mg/m^2).
- Enrolment to the phase I study is complete with no DLTs observed.
- PK analysis indicates no interaction between the two agents.
- Analysis of response rate for phase I component (secondary objective) is currently underway.
- The phase II component of the study is currently underway and more than 30 US-based sites affiliated with the HOG network have been activated.

References

Kremmidiotis *et al.* Molecular Cancer Therapeutics, 9, June 2010.
Ellis *et al.* Molecular Cancer Therapeutics 11, February 2012.
Rischin *et al.* Clinical Cancer Research, 17 (15), August 2011.
O'Donnell *et al.* Journal of Clinical Oncology, 26 (10), April 2008.