

Phase I/II study of BNC105P in combination with everolimus or following everolimus for progressive metastatic renal cell carcinoma following prior tyrosine kinase inhibitors. (Hoosier Oncology Group)

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Background

- BNC105 (Fig. 1A) is a small molecule that acts as a tubulin depolymerization agent.
- BNC105P is a phosphorylated prodrug form (Fig. 1B) 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)
- Up regulation of the mTOR pathway has been identified as a 'survival' response by the tumor to hypoxic insult. It follows that 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 in up to 21 US-based sites.

Drug Substance / Drug Product

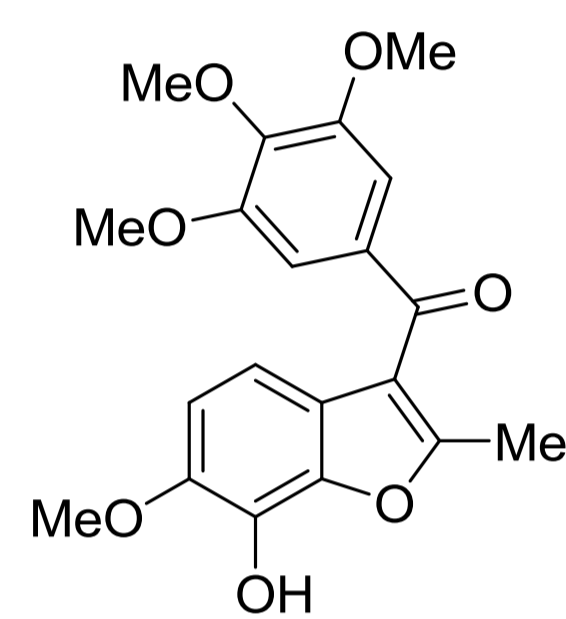


Fig 1A: Structure of BNC105 (active agent)

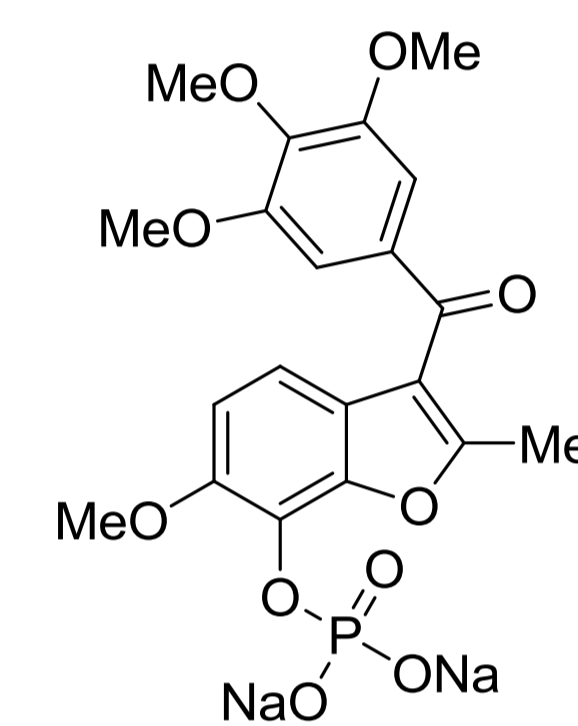


Fig 1B: Structure of BNC105P (phosphate prodrug)

BNC105P Solution For Injection is a sterile solution containing 10 mg/mL of the prodrug in saline.

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 from registration.

Exploratory Objective

To determine the correlation of PFS with biomarkers. Trial registration number: NCT01034631 (clinicaltrials.gov)

Key Eligibility

Histological or cytological proof of component (any percent) of clear cell RCC (renal cell carcinoma). No component of collecting duct, medullary, or sarcomatoid histology.
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. (> 450 and ≤ 500 msec, subject to cardiology review.)
White blood cell count (WBC) > 3.5 K/mm³, hemoglobin > 8.5 g/dL, platelets > 100 K/mm³, absolute neutrophil count (ANC) > 1.5 K/mm³, 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 of the study.
No use of full dose, therapeutic anti-coagulation with warfarin or related anti-coagulants.
No uncontrolled hypertension, BP $> 150/100$ mmHg 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 prior to registration.
No grade 2 or greater peripheral neuropathy.

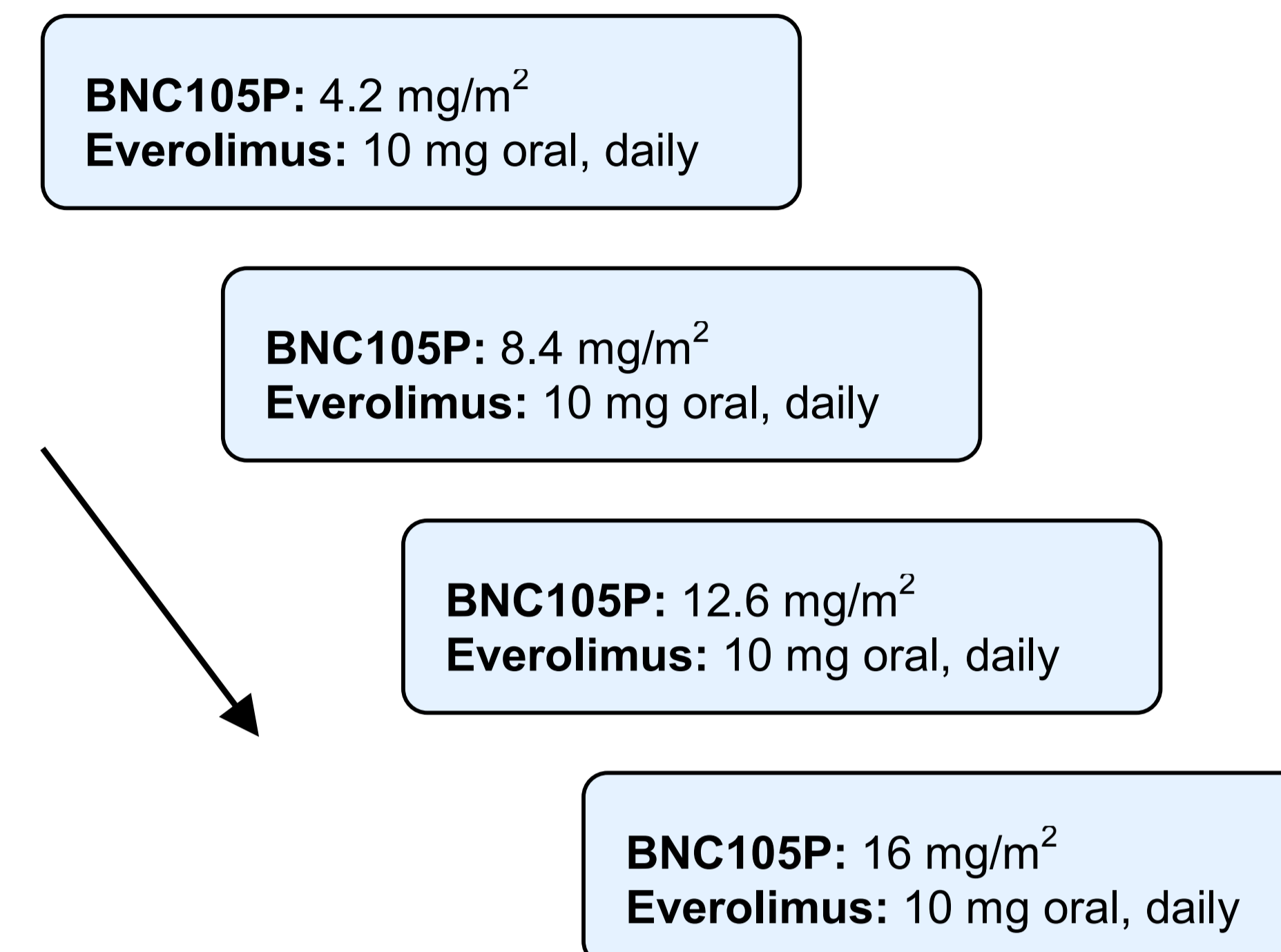
Study Design

Phase I (combination)

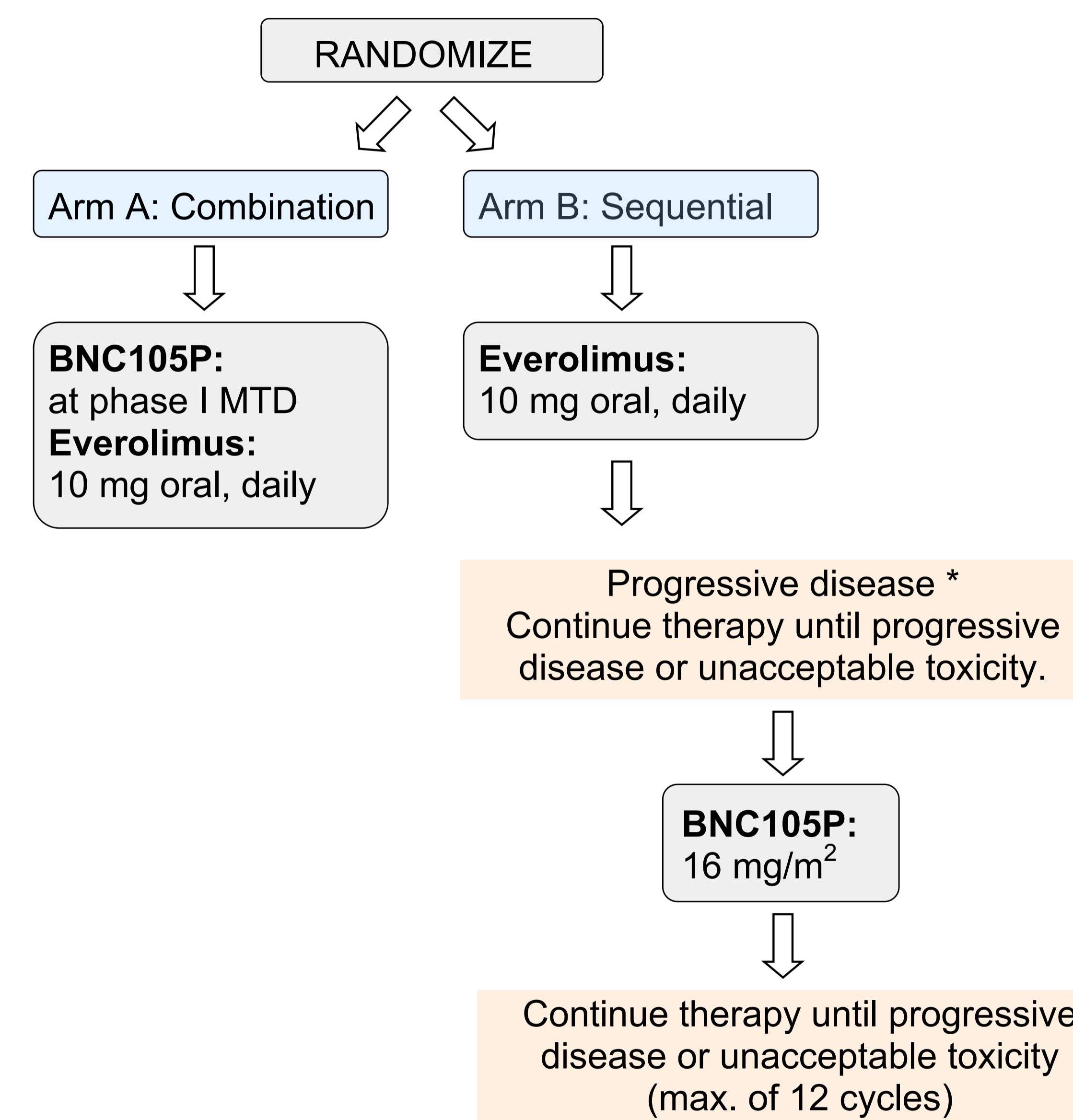
4 dose levels of BNC105P, 3x3 design, N=12-24

Administered until evidence of progressive disease or unacceptable toxicity.

PK assessment.



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



* Allows comparison of everolimus single agent to combination. In Arm B, those patients progressing on everolimus therapy will be offered BNC105P, allowing evaluation of BNC105P following TKI and everolimus use.

Drug Administration

BNC105P is administered by IV injection over 10 min on Day 1 & Day 8 every 21 days.
Everolimus is orally administered (10 mg) daily, with a 7 day lead in prior to administration of BNC105P.

Statistical Considerations

Phase I sample size consideration

Up to 24 patients in 4 cohorts of 3-6 patients each, will be enrolled during the Phase I. The MTD is defined at the dose level where $< 33\%$ of the subjects experience a DLT (i.e. 0/3 or 1/6).

Phase II sample size consideration

The randomized phase II trial portion will be powered to detect an improvement in 6-month PFS from 36% with everolimus to 60% with the combination of everolimus plus BNC105P. 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 to detect a difference between the null hypothesis that both group proportions are 36% and the alternative hypothesis that the proportion in the combination group is 60%, using a one-sided Chi-square test with continuity correction and with a significance level of 0.05. Assuming that $\sim 10\%$ 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 [BUN], total carbon dioxide [CO₂], albumin, total bilirubin, alkaline phosphatase, AST, ALT), phosphorus and electrolytes (total calcium, chloride, potassium, sodium).
LDH, Lipid Panel.
ECG : For phase I - pre-treatment and 6 hours after BNC105P infusion on Days 1 and 8 of Cycle 1. For Phase 2 - Day 1 Cycle 2 pre-treatment only.
Urine analysis.

Trial Status

Up to 21 US-based sites affiliated with the HOG network will be activated.

First patient visit occurred in April 2010.

As of mid-May 2011, there have been NO observed Dose Limiting Toxicities.

Enrolment to the phase I study is near complete.

The phase II component of the study will soon commence; clinical operational items are being finalized with all participating sites.

Summary

- Enrolment to the phase I study is near complete.
- The phase II component of the study will soon commence.

References

Kremmidiotis *et al.* Molecular Cancer Therapeutics, 9 (6), June 2010.