A Phase I/II Trial of BNC105P with Everolimus in Metastatic Renal Cell Carcinoma


Abstract

Purpose: BNC105P inhibits tubulin polymerization, and preclinical studies suggest possible synergy with everolimus. In this phase I/II study, efficacy and safety of the combination were explored in patients with metastatic renal cell carcinoma (mRCC).

Experimental Design: A phase I study in patients with clear cell mRCC and any prior number of therapies was conducted using a classical 3+3 design to evaluate standard doses of everolimus with increasing doses of BNC105P. At the recommended phase II dose (RP2D), patients with clear cell mRCC and one to two prior therapies (including >1 VEGF-TKI) were randomized to BNC105P with everolimus (arm A) or everolimus alone (arm B). The primary endpoint of the study was 6-month progression-free survival (6MPFS). Secondary endpoints included response rate, PFS, overall survival, and exploratory biomarker analyses.

Introduction

Current treatment algorithms for metastatic renal cell carcinoma support use of vascular endothelial growth factor (VEGF)-directed therapies in the first-line setting for the majority of patients (e.g., patients with good- and intermediate-risk disease; ref. 1). For patients who progress on these agents, phase III data exist to support several strategies including continued VEGF-directed therapy (e.g., axitinib) or with an inhibitor of the mTOR (e.g., everolimus; refs. 2, 3). Even with various permutations of these agents, mRCC remains an incurable disease. One attempted strategy has been to combine existing VEGF- and mTOR-directed therapies—to date, these efforts have shown concerning toxicity and/or a lack of efficacy (4, 5). Novel agents that are combinable and synergistic with existing therapies are therefore actively sought.

In the current study, the combination of everolimus with a vascular disrupting agent (VDA) is explored. VDAs are distinct from currently approved VEGF-directed therapies in that they disrupt existing tumor blood vessels rather than suppressing neovasculature (6). As a result, these agents cause tumor vascular collapse and cessation of blood flow leading to tumor ischemia and necrosis (7). Preclinical evaluation of combination regimens involving a VDA and an mTOR inhibitor demonstrated synergistic activity leading to improved antitumor effects (8, 9). In these studies, combined therapy was more efficacious in reducing endothelial cell sprouting, causing tumor vascular damage, and reducing tumor blood volume.

The novel VDA BNC105P is a disodium phosphate ester produg of BNC105, a tubulin polymerization inhibitor that exhibits a high degree of selectivity for tumor endothelial cells (7). The drug displays >80-fold higher potency against endothelial cells that are actively proliferating or engaged in the formation...
Translational Relevance

Everolimus represents a standard treatment used after failure of VEGF-directed therapy in patients with metastatic renal cell carcinoma (mRCC). The current phase I/II study explores the combination of everolimus with the novel vascular disrupting agent BNC105P. Although the study failed to meet its primary endpoint, correlative studies done in association with this trial suggest that there might be a subset of patients that derive benefit from combination therapy. These patients are defined by dynamic biomarkers including matrix metalloproteinase-9, stem cell factor, sex hormone-binding globulin, and serum amyloid A protein. A prospective study is under development that will explore everolimus with BNC105P in a biomarker-defined subpopulation of patients.

Patients and Methods

Eligibility

For both the phase I and phase II components of the study, patients were required to have histologically confirmed RCC with a clear cell component. Notably, any proportion of clear cell disease was allowed. Patients were further required to have metastatic disease, a Karnofsky performance status (KPS) of ≥70, adequate organ function and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Key exclusion criteria included collecting duct or medullary histology, active brain metastasis, significant cardiovascular events within 6 months, congestive heart failure (left ventricular ejection fraction <50%), and full-dose anticoagulation. Patients may have received any number of prior VEGF-tyrosine kinase inhibitors (VEGF-TKI) before enrollment in the phase I component of the study, but may have received only one to two prior VEGF-TKIs before enrollment in the phase II component. Prior therapy with an mTOR inhibitor was allowed in the phase I component of the study, but prohibited in the phase II component. Aside from these requirements, there were no limits on the cumulative number of prior therapies rendered. Phase I patients were required to consent to pharmacokinetic (PK) sampling.

Phase I design and PK analysis

Everolimus (10 mg) was orally administered daily with a 7-day lead in before the first administration of BNC105P. Patients received BNC105P monotherapy on days 1 and 8 of a 21-day cycle as a 10-minute intravenous (i.v.) injection. BNC105P doses of 4.2, 8.4, 12.6, and 16 mg/m² were explored. A standard 3 + 3 dose-escalation design was followed, where 3 patients were treated in each dose level, with expansion to 6 patients if a dose-limiting toxicity (DLT) was observed. In the case of a second DLT occurring in a 6 patient cohort, no further escalation was to be undertaken and the cohort of one dose level below was to be expanded to confirm that level as the MTD. Dosing continued until evidence of progressive disease or unacceptable toxicity was observed. The follow-up period was 30 days after administration of last dose.

PK samples for BNC105P and everolimus analysis in plasma were obtained before dosing (baseline), at the end of the injection, at 10, 20, 40, 60, and 90 minutes, and at 2, 4, and 6 hours after completion of the injection on days 1 and 8 of cycle 1. PK samples for everolimus analysis in whole blood were obtained before BNC105P dosing, at the end of the injection, at 40 and 60 minutes, and at 2, 4, and 6 hours after completion of the BNC105P injection on days 1 and 8 of cycle 1. Analytes were separated by high-performance liquid chromatography (Shimadzu Scientific Instruments) and the eluates monitored using MS-MS detection (Applied Biosystems API4000 mass spectrometer). All analytical methods adhered to the GLP principles and the FDA guidance on bioanalytical method validation.

Randomized phase II design and biomarker analysis

Patients with mRCC meeting the aforementioned eligibility criteria were randomized in a 1:1 fashion to receive either monotherapy with everolimus at standard doses or the recommended phase II doses for the combination of everolimus with BNC105P identified from the lead-in phase I trial. Patients were treated until progressive disease or unacceptable toxicity was observed. Dose reductions were permitted for each agent independently based on investigator attribution of toxicity, and if no attribution could be made, then doses of both drugs were reduced. Patients requiring more than two dose reductions were removed from the study. Doses of everolimus were reduced from 10 mg oral daily to 5 mg oral daily to 5 mg oral every other day. Doses of BNC105P were reduced from 16 mg/m² to 12.6 mg/m² to 8.4 mg/m². Notably, at the time of progression, patients receiving everolimus monotherapy were allowed to continue on BNC105P monotherapy until the time of progression. A starting dose of 16 mg/m² was used, again with the same dose reductions used.

Blood draws for biomarker assessments in the phase II component of the study were prespecified and optional. Patients randomized to receive everolimus with BNC105P received blood draws on days 1 and 8 of therapy immediately before BNC105P, 1 to 3 hours following BNC105P and at the time of progression. Patients randomized to receive everolimus alone did not receive these blood draws at baseline, but rather received blood draws at identical time points at the time they crossed over onto BNC105P monotherapy. Plasma samples from 44 evaluable patients enrolled in the trial were used to determine plasma concentrations for 40 exploratory biomarkers (Supplementary Table S1). Biomarker concentration determinations were carried out by Myriad RBM using Multi-Analyte Profiling Technology, which is based on microsphere immuno-multiplexing with LumineX xMAP technology. Briefly, microsphere beads were conjugated to antibodies encoded with unique fluorescent signatures that are specific to each
biomarker of interest. Beads and plasma samples were incubated to allow for target binding followed by the addition of detection reagents and fluorescent reporter molecules. Fluorescence generated for each unique biomarker signature in proportion to the biomarker concentration in the sample is acquired using the LumineX xMAP instrumentation with biomarker concentration in samples determined from standard curves for each individual biomarker. Nonparametric tests (Wilcoxon–match–pairs sign rank test) were used to compare biomarker values before administration and following administration of BNC105. Median values for each biomarker (expressed as a ratio to pretreatment concentrations) were used as the cut-points for stratification of patients into two groups which were then evaluated for correlation with the efficacy endpoint of 6-month PFS as previously described (11). Time-to-event analysis was performed using Kaplan–Meier curves and results compared using log-rank test. All patients were given the option to submit tissue (either frozen or paraffin embedded) from diagnostic or surgical procedures for RCC.

Clinical assessments

Patients were assessed for safety by means of monitoring for adverse events (AE) that were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Response was assessed using RECIST 1.0 criteria at baseline and after every third cycle. Treatment emergent adverse events (TEAE) were defined as new or worsening AEs (both drug and non-drug related), which commenced or worsened, on or after the time of first administration of the study drug.

Statistical analysis

As noted, the phase I component of the study utilized a classical 3 + 3 design to identify the MTD for phase II assessment. The primary endpoint of the randomized phase II trial was 6-month progression-free survival (6MPFS). With 61 patients per group, there was estimated to be 80% power to detect an improvement in 6MPFS from 36% on the control arm (everolimus alone) to 60% on the experimental arm (the combination of everolimus with BNC105P) using one-sided $\chi^2$ test with continuity correction ($\alpha = 0.05$). A 6-month landmark was used to ascertain a clinical benefit more rapidly and facilitate a decision regarding further study of the combination. Patients were stratified by Memorial Sloan Kettering Cancer Center (MSKCC) risk group (good, intermediate and poor) and number of prior regimens (1 or > 1). Assuming roughly 10% of patients would be ineligible for the primary endpoint, a target total enrollment of 134 patients was set.

Secondary endpoints in the phase I component of the study included PK parameters, which were evaluated using descriptive statistics. Secondary endpoints in the phase II component included cumulative PFS and overall survival (OS), summarized using the Kaplan–Meier method, as well as overall response rate (ORR) and AEs.

Results

Patient characteristics

A total of 15 patients were enrolled in the phase I component. Twelve of the 15 patients completed at least one cycle of combination therapy, and the 3 patients who did not complete one cycle were replaced at the same dose level. The median age of this cohort was 62 years, with 9 male patients (60%) and 6 female patients (40%). The majority of the patients enrolled were white (13 patients, or 87%), and the remainder were African American. In the randomized phase II study, a total of 139 patients were randomized. One patient was deemed ineligible after randomization but before initiation of therapy—characteristics of the remaining 138 patients are listed in Table 1. Ultimately, 69 patients and 67 patients were evaluable for safety and efficacy in the combination therapy arm and everolimus monotherapy arm, respectively (Fig. 1). Both treatment arms were balanced with respect to baseline demographic factors and clinicopathologic criteria. The median age of the overall study population was 63 years, with the majority (76%) being male. As in the phase I experience, the majority of patients were white (87%), and the majority of patients had a KPS ranging from 80% to 100 (93%). There was a similar distribution of patients by MSKCC risk group across treatment arms; approximately 24% of patients were characterized as good-risk, whereas 67% were characterized as intermediate risk. Only 9% of patients were noted to be poor-risk. The most frequent sites of metastasis amongst patients enrolled in the phase II study were: (i) lung (80%), (ii) bone (33%), and liver (19%). The extent of prior therapy was similar between arms. Notably, nearly one-third of patients had received four or more prior treatments.

### Table 1. Patient demographics in the phase II component of the DisturpTOR-1 study (arm A, everolimus with BNC105P; arm B, everolimus monotherapy)

<table>
<thead>
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<th>Total (%)</th>
<th>Arm A (%)</th>
<th>Arm B (%)</th>
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</tr>
</thead>
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<tr>
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<td>60 (9)</td>
<td>61 (9)</td>
<td>63 (9)</td>
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<tr>
<td>Mean (SD)</td>
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<td>70 (7)</td>
<td>70 (7)</td>
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<tr>
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<tr>
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<td></td>
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<td>61 (88)</td>
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<td>5 (7)</td>
<td>5 (7)</td>
</tr>
<tr>
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<td>1 (1)</td>
<td>0 (0.00)</td>
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<td>MSKCC Risk Group</td>
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<tr>
<td>Good</td>
<td>33 (24)</td>
<td>17 (24.64)</td>
<td>16 (23.9)</td>
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<td>Intermediate</td>
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<td>45 (65.22)</td>
<td>47 (68.12)</td>
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<tr>
<td>Poor</td>
<td>13 (9)</td>
<td>7 (10.14)</td>
<td>6 (8.70)</td>
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<td>Metastatic site</td>
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<tr>
<td>Lung</td>
<td>111 (80)</td>
<td>57 (83)</td>
<td>54 (78)</td>
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<tr>
<td>Liver</td>
<td>26 (19)</td>
<td>13 (19)</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Bone</td>
<td>45 (32)</td>
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<td>24 (35)</td>
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<tr>
<td>Brain</td>
<td>8 (6)</td>
<td>5 (4)</td>
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<tr>
<td>Number of prior therapies</td>
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<tr>
<td>1</td>
<td>27 (20)</td>
<td>14 (20)</td>
<td>13 (19)</td>
</tr>
<tr>
<td>2</td>
<td>42 (30)</td>
<td>24 (35)</td>
<td>18 (26)</td>
</tr>
<tr>
<td>3</td>
<td>25 (18)</td>
<td>10 (14)</td>
<td>15 (22)</td>
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<tr>
<td>&gt;4</td>
<td>44 (33)</td>
<td>21 (30)</td>
<td>23 (33)</td>
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</table>
respect to the extent of prior VEGF-TKI therapy, 85% had received one prior VEGF-TKI, while the remainder received two.

**Phase I study: efficacy and safety**

No protocol-defined DLTs (drug-related, during cycle 1) were observed in any of the phase I subjects and thus there was no expansion in any of the dose level cohorts outside of the highest dose level (16 mg/m²). Thus, the combination of everolimus at 10 mg oral daily with BNC105P at 16 mg/m² on days 1 and 8 on a 21-day cycle was identified as the recommended phase II dose (RP2D). Toxicities observed on study that were deemed to be drug related (either single agent or combination) included single grade 3 events of anemia and pericardial effusion. Grade 2 events (more than 1 occurrence) of fatigue, anemia, and oral mucositis were also observed. TEAEs considered to have a potential causal relationship to either study drug (possibly, probably, or definitely related to study drug) are listed in Supplementary Table S2. No objective responses were observed, but SD was observed in 8 patients with a median time on therapy of 11 cycles (33 weeks) and a range of 5 to 24 cycles.

**Phase I study: PK results**

PK analysis was performed on plasma from the 14 patients who received study treatment. The geometric mean half-life of BNC105P, averaged across all patients for both day 1 and day 8, was 0.08 hours (5 minutes). The geometric mean half-life of BNC105 was 0.32 hours (19 minutes). The elimination rate of BNC105 immediately postdose appears to be first-order, with the rate becoming slower by 30 minutes postdose. The concentration profiles were similar for the two treatment days. There was no trend observed in the plasma levels of either analyte between the day 1 and day 8 profiles, indicating no change in metabolism across the two administrations of the drug in cycle 1.

Everolimus was administered daily in the evening. PK sampling was performed during clinic visits on the day of BNC105P administration. The mean concentration was approximately constant over the 6-hour collection interval, with an overall mean of 17.8 ng/mL. This value is consistent with previously reported results, where the half-life was reported as 26 to 38 hours, and the mean trough concentration at steady state was 13.2 ng/mL in patients who received 10 mg everolimus daily (12).

**Phase II study: efficacy and safety**

A mean of 7.46 and 6.01 cycles of combination therapy and everolimus monotherapy was rendered in each arm, respectively. At the time of last follow-up, the maximum number of cycles of combination therapy rendered was 31, as compared with 20 cycles of everolimus monotherapy. The primary outcome measure, 6MPFS, was similar in both study arms (33.82% with...
Combination therapy vs. 30.30% with everolimus monotherapy; 
\( P = 0.66 \). One complete response and one partial response on 
combination therapy were observed, and two partial responses with 
everolimus monotherapy were observed. At the time of last 
follow-up, responses were ongoing for a duration in excess of 12 
months. As depicted in Fig. 2, there was no difference in median 
PFS. Furthermore, no differences were seen in median PFS amongst 
patient subgroups stratified by prespecified criteria, including 
MSKCC risk score and number of prior VEGF-TKIs. In an 
explanatory analysis of clinical outcome based on sites of 
metastasis, an improvement in median PFS was seen with 
combination therapy amongst patients with liver metastasis (6.6 
months vs. 2.8 months, Fig. 3). These results should be interpreted 
with caution, however, given the limited number of patients in the 
analysis.

A total of 33 patients were ultimately crossed over from everolimus 
monotherapy to monotherapy with BNC105P. The demographics of 
this population did not vary significantly from the overall study population—the median age of this group was 66 years, 
and 76% of the patients were male. Amongst 25 patients in 
this subset evaluable for response, SD was recorded as the best 
response in 20 patients (80%). Median time to progression was 
1.8 months (95% confidence intervals; CI, 1.74–2.04; Supple-
mental Fig. 1S).

AEs present in more than 10% of the study population in the 
phase II experience are shown in Table 2. The most frequent 
clinical AEs were fatigue, dyspnea, cough, diarrhea, and mucositis. The most frequent laboratory abnormalities were hyper-
cholesterolemia, hypertriglyceridemia, and hyperglycemia. 
Toxicities were similar in both treatment arms. As many of 
these toxicities (e.g., mucositis, dyspnea, elevated lipids, and 
hyperglycemia) are frequently encountered with everolimus, 
it was felt that the majority of adverse events were attributable 
to everolimus as opposed to BNC105P. The majority of toxic-
ities were grade 1/2. Two deaths encountered with combination therapy were 
deemed potentially related to protocol-based therapy secondary 
to pneumonitis and infection, respectively. Given the lack of 
preneumonitis and infection seen in previous studies of BNC105P 
and the occurrence of these adverse events in previous studies of 
everolimus, they were presumably related to the latter.

**Phase II study: biomarker analysis**

As noted in Patients and Methods, serum was collected for 
prospective biomarker analyses in patients receiving systemic 
therapy with BNC105P (both as combination therapy and as 
monotherapy following progression on everolimus alone). Blood 
was collected before and after administration of drug, and thus 
data presented herein reflect the change in biomarker level before 
and after drug administration. Significant associations were noted 
between the change in four biomarkers (above and below the 
median value) and PFS (Fig. 4). Specifically, an increase in matrix 
metalloproteinase-9 (MMP-9) and stem cell factor (SCF) 
was associated with an improvement in PFS. Changes in MMP-9 
correlated with changes in SCF. In contrast, a decrease in sex 
hormone-binding globulin (SHBG) and serum amyloid P-com-
ponent (SAP) was associated with improved PFS. Changes in 
SHBG correlated with changes in SAP. Patients that were prog-
gression-free at 6 months correlated with increased MMP-9 and SCF 
or decreased SHBG and SAP. Selection of patients based on such 
changes in these four biomarkers enriches for patients that are 
progression free at 6 months (from 36% in the unselected pop-
ulation to 60% in the selected population).

**Discussion**

The phase I component of the study identified a MTD of 
16 mg/m² for BNC105P in combination with the standard 
dose of everolimus, with no DLTs observed. Evaluation in 
the randomized phase II setting suggested no significant differ-
ence in 6MPFS with the combination of everolimus and 
BNC105P as compared with everolimus monotherapy. Further-
more, no significant differences in cumulative PFS, OS, and ORR 
were seen. Notably, it did not appear that BNC105P added 
substantially to the toxicity profile of everolimus, with most 
toxicities seen with combination therapy attributable to the 
latter. Exploratory biomarker analyses identified associations 
between clinical outcome with combination therapy and MMP-
9, SCF, SAP, and SHBG. Thus, although the study failed to meet 
its primary endpoint, further exploration of these correlative 
results (perhaps in the context of a biomarker-driven trial) might 
be warranted.
There is currently equipoise regarding the optimal second-line treatment of mRCC after failure of first-line VEGF-directed agents. The strategy of combination therapy is one of three potential avenues to improving outcomes in pretreated patients. A second potential option is to evaluate novel therapies in comparative designs. Impressive early data for the programmed death-1 inhibitor nivolumab have led to a phase III comparison of nivolumab versus everolimus in the second-line setting (13–15). Similarly, encouraging data from a phase I trial evaluating the dual VEGFR2/MET inhibitor cabozantinib in patients with mRCC have led to a phase III study also directly comparing the agent to everolimus (16, 17). Notably, even if these studies are positive and result in therapeutic approval, everolimus will remain a part of the therapeutic continuum. Thus, the approach of evaluating combinations that may enhance the activity of the drug remains valid.

The third potential avenue is evaluation of therapies in prospective biomarker-based trials. In the current study, changes in several serum biomarkers with BNC105P therapy have been associated with improved clinical outcome—before this study, biomarkers related to VDA response have been poorly characterized. Increased expression of MMP-9 correlates with poor prognostic variables in patients with RCC, and may predict metastasis in patients with localized disease (18–20). From a mechanistic standpoint, MMP-9 may contribute to increased tumor angiogenesis (21). SCF binds to c-Kit, a putative target of VEGF-TKIs such as sorafenib (22). Several studies have shown a correlation between clinical outcome and SCF, and mutations in the substrate binding pocket of SCF have been implicated in conferring resistance to TKIs (23, 24). Less is known about the mechanistic role of the remaining two biomarkers, SAP and SHBG, in the pathogenesis of RCC, although some studies have suggested a prognostic role of SAP in the disease (25). In an exploratory analysis, the four biomarkers noted herein were assessed in combination to generate a potential signature for response. With selection of patients that had (1) a rise in MMP-9 and SCF and (2) a fall in SHBG and SAP, approximately 60% of patients were progression free at 6 months. Amongst patients that failed to meet this definition, only 5% were progression free at 6 months. In a prospective trial of everolimus with BNC105P, one could envision enriching the study for those patients who meet this stringent biomarker characterization after a test dose of BNC105P.

Table 2. Adverse events present in 10% or more of the study population in the phase II component of the DisrupTOR-1 study (arm A, everolimus with BNC105P; arm B, everolimus monotherapy)

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<th>Arm B (N = 67)</th>
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</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>5.8</td>
<td>10</td>
</tr>
<tr>
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<td>10</td>
<td>0</td>
<td>10</td>
<td>14.5</td>
<td>4</td>
</tr>
<tr>
<td>Taste alteration</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>7.2</td>
<td>10</td>
</tr>
<tr>
<td>Episiotis/respiratory tract hemorrhage</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>8.7</td>
<td>8</td>
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</table>

There is currently equipoise regarding the optimal second-line treatment of mRCC after failure of first-line VEGF-directed agents. The strategy of combination therapy is one of three potential avenues to improving outcomes in pretreated patients. A second potential option is to evaluate novel therapies in comparative designs. Impressive early data for the programmed death-1 inhibitor nivolumab have led to a phase III comparison of nivolumab versus everolimus in the second-line setting (13–15). Similarly, encouraging data from a phase I trial evaluating the dual VEGFR2/MET inhibitor cabozantinib in patients with mRCC have led to a phase III study also directly comparing the agent to everolimus (16, 17). Notably, even if these studies are positive and result in therapeutic approval, everolimus will remain a part of the therapeutic continuum. Thus, the approach of evaluating combinations that may enhance the activity of the drug remains valid.

The third potential avenue is evaluation of therapies in prospective biomarker-based trials. In the current study, changes in several serum biomarkers with BNC105P therapy have been associated with improved clinical outcome—before this study, biomarkers related to VDA response have been poorly characterized. Increased expression of MMP-9 correlates with poor prognostic variables in patients with RCC, and may predict metastasis in patients with localized disease (18–20). From a mechanistic standpoint, MMP-9 may contribute to increased tumor angiogenesis (21). SCF binds to c-Kit, a putative target of VEGF-TKIs such as sorafenib (22). Several studies have shown a correlation between clinical outcome and SCF, and mutations in the substrate binding pocket of SCF have been implicated in conferring resistance to TKIs (23, 24). Less is known about the mechanistic role of the remaining two biomarkers, SAP and SHBG, in the pathogenesis of RCC, although some studies have suggested a prognostic role of SAP in the disease (25). In an exploratory analysis, the four biomarkers noted herein were assessed in combination to generate a potential signature for response. With selection of patients that had (1) a rise in MMP-9 and SCF and (2) a fall in SHBG and SAP, approximately 60% of patients were progression free at 6 months. Amongst patients that failed to meet this definition, only 5% were progression free at 6 months. In a prospective trial of everolimus with BNC105P, one could envision enriching the study for those patients who meet this stringent biomarker characterization after a test dose of BNC105P.
Several limitations of the reported study should be noted. First, although the intent of the study was to transition patients receiving everolimus monotherapy to BNC105P monotherapy, this crossover did not take place in the majority of patients. This limits the ability to infer any potential benefit of BNC105P in the everolimus-refractory patient. Second, there was significant heterogeneity in the number of prior lines of therapy rendered. With nearly one-third of patients receiving four or more prior systemic treatments, it is challenging to ascertain whether imbalances in this regard may have led to the null difference in the treatment arms. Third, the study aimed to demonstrate an improvement in 6MPFS, a somewhat uncharacteristic primary endpoint amongst studies in mRCC. Although this may be a moot point given a lack of significant differences in other clinical outcomes (e.g., PFS, OS, and ORR), selection of a different endpoint may have impacted the design and enrollment of the study. The investigators felt 6MPFS to be justified given data from the phase III AXIS and RECORD-1 trials, evaluating axitinib and everolimus, respectively. When specifically considering the subset of patients with one prior VEGF-TKI, a median PFS of 4.8 and 5.4 months was observed, respectively. Finally, a major limitation of the noted biomarker analyses is that no blood was collected on the control arm (everolimus alone) at baseline. As noted, the protocol stipulated blood collection at the start of therapy with the combination of agents or with BNC105P monotherapy. Of note, further correlative studies are underway using tissue collected from both control and experimental arms using the NanoString multigene assay, a platform that has been applied in several other malignancies (26, 27). In contrast with the serum studies reported herein, by inclusion of specimens from the control arm, these studies may be both prognostic and predictive.

Despite these limitations, the current study adds to a relatively scant literature documenting the activity of an investigational compound in concert with everolimus. There have been previous unsuccessful attempts to demonstrate a benefit with the combination of VEGF- and mTOR-directed treatments for mRCC. The RECORD-2 trial, for instance, compared the combination of bevacizumab and everolimus with the standard combination of bevacizumab with IFNα (5). The study failed to meet its primary endpoint, showing no difference in PFS with the two regimens. The randomized phase III INTORACT trial compared bevacizumab and temsirolimus (an intravenous mTOR inhibitor) with bevacizumab and IFNα, and similarly showed no significant difference in clinical outcome (4). Although the DisruptOR-1 trial showed no benefit with the addition of BNC105P to everolimus in the overall study population, a narrower assessment in a biomarker-driven population may be a potential avenue forward for this agent.

Disclosure of Potential Conflicts of Interest
S. Pal is a consultant/advisory board member for Novartis and Bionomics. S. Bhatia reports receiving speakers bureau honoraria from GlaxoSmithKline. C.I. Sweeney and N.M. Hahn are consultants/advisory board members for Bionomics. A. Leske has ownership interest (including patents) in Biomnis. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Pal, S. Bhatia, R. Hauke, J. Sarantopoulos, G. Sonpavde, S. Richey, T. Breen, D.C. Bibby, J. Simpson, T. Hutson
Other (e.g., general management, writing and editing): S. Pal, S. Bhatia, J. Sarantopoulos, R. Hauke, C.J. Sweeney, N.M. Hahn, G. Sonpavde, S. Richey, T. Breen, D.C. Bibby, J. Simpson, T. Hutson

Figure 4.
PFS in patients treated with everolimus with BNC105P stratified by change in serum biomarkers above or below median values. Serum biomarkers include MMP-9 (A), SCF (B), SHGB (C), and SAP (D).
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Pal, R. Kanesvaran, T. Breen, E. Doolin, J. Simpson

References


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