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Original Article

A Phase 2 Clinical Trial of Everolimus Plus Bicalutamide for Castration-Resistant Prostate Cancer

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BACKGROUND: The mammalian target of rapamycin (mTOR) pathway is up-regulated in castration-resistant prostate cancer (CRPC). Nevertheless, inhibition of mTOR is ineffective in inducing apoptosis in prostate cancer cells, likely because of the compensatory up-regulation of the androgen receptor (AR) pathway. **METHODS:** Patients who were eligible for this study had to have progressive CRPC with serum testosterone levels <50 ng/dL. No prior bicalutamide (except to prevent flare) or everolimus was allowed. Treatment included oral bicalutamide 50 mg and oral everolimus 10 mg, both once daily, with a cycle defined as 4 weeks. The primary endpoint was the prostate-specific antigen (PSA) response (≥30% reduction) from baseline. A sample size of 23 patients would have power of 0.8 and an α error of .05 (1-sided) if the combination had a PSA response rate of 50% versus a historic rate of 25% with bicalutamide alone. **RESULTS:** Twenty-four patients were enrolled. The mean age was 71.1 years (range, 53.0-87.0 years), the mean PSA level at study entry was 43.4 ng/dL (range, 2.5-556.9 ng/dL), and the mean length of treatment was 8 cycles (range, 1.0-23.0 cycles). Of 24 patients, 18 had a PSA response (75%; 95% confidence interval [CI], 0.53-0.90), whereas 15 (62.5%; 95% CI, 0.41-0.81) had a PSA decrease ≥50%. The median overall survival was 28 months (95% CI, 14.1-42.7 months). Fourteen patients (54%; 95% CI, 0.37-0.78) developed grade 3 (13 patients) or grade 4 (1 patient with sepsis) adverse events that were attributable to treatment. **CONCLUSIONS:** The combination of bicalutamide and everolimus has encouraging efficacy in men with bicalutamide-naive CRPC, thus warranting further investigation. A substantial number of patients experienced everolimus-related toxicity. ***Cancer*** **2016;122:1897-904**.

KEYWORDS: castration-resistant prostate cancer, everolimus, bicalutamide, mammalian target of rapamycin (mTOR), urology.

INTRODUCTION

Over 80% of patients with newly diagnosed prostate cancer (CaP) have localized disease, with treatment options between the 2 standard forms of curative therapy: radical prostatectomy or radiation therapy. Approximately 1/3 of patients who receive local therapies will have a biochemical recurrence.[1,2] Some of these patients can be salvaged with either radiotherapy or (rarely) surgery, depending on previous therapy received. The remaining patients with recurrent CaP and those who present with metastatic CaP are usually treated with androgen-deprivation therapy (ADT), which initially is highly effective.[3] However, most patients will develop castration-resistant CaP (CRPC) within 18 to 24 months.[4] Second-line therapy with an androgen receptor (AR) modulator, such as bicalutamide, is associated with a response rate around 25% and a duration of response of a few months.[3,5] Although new medications, such as enzalutamide and abiraterone, have been approved after bicalutamide, long-term survival is extremely rare. Most patients will become resistant to the treatment, and at least 27,000 patients die each year from this disease.[6] Therefore, there is a substantial need to improve upon new treatment options.

Several mechanisms have been proposed to explain castration-resistance, such as overexpression of AR, AR mutation, autocrine or paracrine production of androgen, and alternative signaling pathways, among others. We previously reported up-regulation of the mammalian target of rapamycin (mTOR) pathway in CRPC cell lines and in CaP cells treated with ADT.[7] mTOR is a key serine-threonine kinase that regulates protein synthesis, cell growth, proliferation, angiogenesis, and survival. However, a previous study demonstrated that inhibition of the mTOR signaling pathway also up-regulated the AR

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signaling pathway.[7] This compensatory mechanism explained why an mTOR inhibitor alone has little therapeutic effect in CRPC.[8] We observed that inhibition of the mTOR signaling pathway up-regulated the AR signaling pathway, which compensated for the therapeutic effect of an mTOR inhibitor.[7] In addition, bicalutamide inhibited AR transcriptional activity stimulated by rapamycin without affecting inhibition of the mTOR pathway. Simultaneous treatment with the mTOR inhibitor rapamycin and the AR inhibitor bicalutamide apparently enhanced growth inhibition by rapamycin in both androgen-dependent and independent sublines of LNCaP cells, although bicalutamide had no effect on the growth of CRPC cells as a single agent. Similar synergistic effects of the combination of an AR antagonist and an mTOR antagonist also were observed with in vivo xenograft models.[9-11]

A similar concept of targeting the estrogen receptor (ER) and mTOR pathways was used in the treatment of breast cancer with everolimus, in which sensitivity to hormone therapy was restored by reestablishing levels of ER and ER-inducible target genes. This resulted in the enhancement of sensitivity to tamoxifen and prevention of the development of resistance to hormone therapy by inducing apoptosis in long-term hormone-deprived cells.[12] Efficacy had been established from the Initial Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study, which evaluated the addition of everolimus to an aromatase inhibitor, exemestane, in postmenopausal women with ER-positive/human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer who were refractory to nonsteroidal aromatase inhibitors.[13]

On the basis of these preclinical studies and a similar concept from the BOLERO-2 study, we evaluated the combination of bicalutamide and everolimus (RAD001; an mTOR inhibitor) in treating CRPC. We hypothesized that simultaneous blockade of the mTOR and AR pathways would be synergistic against CRPC cells and that this could be demonstrated in a clinical trial. The primary objective of this trial was to determine the prostate-specific antigen (PSA) response rate of bicalutamide plus everolimus in the treatment of CRPC after the first-line ADT. This trial is registered at clinicaltrials.gov as National Clinical Trial NCT00814788.

MATERIALS AND METHODS

Patient Eligibility

Patients were eligible for enrollment if they were aged >18 years, had a histologically or cytological confirmed diagnosis of CaP, and had castration levels of testosterone (<50 ng per deciliter or 1.7 nmol/L) within 3 months before registration. Patients were required to have CaP that was deemed castration-resistant by: 1) progression of unidimensionally measurable disease assessed within 42 days before initial administration of drug, 2) progression of evaluable but not measurable disease assessed within 42 days before the initial administration of drug for PSA evaluation and for imaging studies, or 3) at least 2 consecutive rises in PSA measured at least 1 week apart. Patients who had biochemically recurrent or metastatic prostate cancer (M0 and M1) were eligible. Patients must have remained on ADT; and they were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2, adequate vital organ function, and adequate bone marrow function.

Exclusion criteria for the study included: any hormone therapy other than ADT (except to prevent flare) or mTOR inhibitors. Patients with the following conditions also were excluded from this study: uncontrolled, serious, concurrent illness; receiving antiretroviral therapy for human immunodeficiency virus infection; and any major surgery or significant traumatic injury within the previous 4 weeks of the start of study drug. Patients who were receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent also were excluded. A complete list of inclusion and exclusion criteria are provided in the protocol (see online supporting information).

Study Design and Treatment

This clinical trial was originally designed as a phase 1b, lead-in safety trial followed by a randomized, double-blind, placebo-controlled phase 2 trial in patients with CRPC. Because there was an administrative delay in obtaining matched placebo tablets, this trial was converted to a single-arm phase 2 trial comparing results with a historic control of bicalutamide as second-line hormone therapy. During the lead-in safety trial, 8 patients were recruited at oral bicalutamide 50 mg daily plus oral everolimus 10 mg once daily. Each cycle was defined as 4 weeks. At each cycle, patients were evaluated clinically for side effects and response, and they underwent laboratory testing (PSA, complete blood count, and comprehensive metabolic panel). Lactate dehydrogenase measurement was not part of the trial. If patients had measurable lesions, then imaging studies were performed every 2 cycles. If patients did not have any measurable lesions, then imaging studies were not required unless clinically indicated. After 4 cycles, patients were followed every 2 cycles (8 weeks). After no grade ≥3 toxicities were

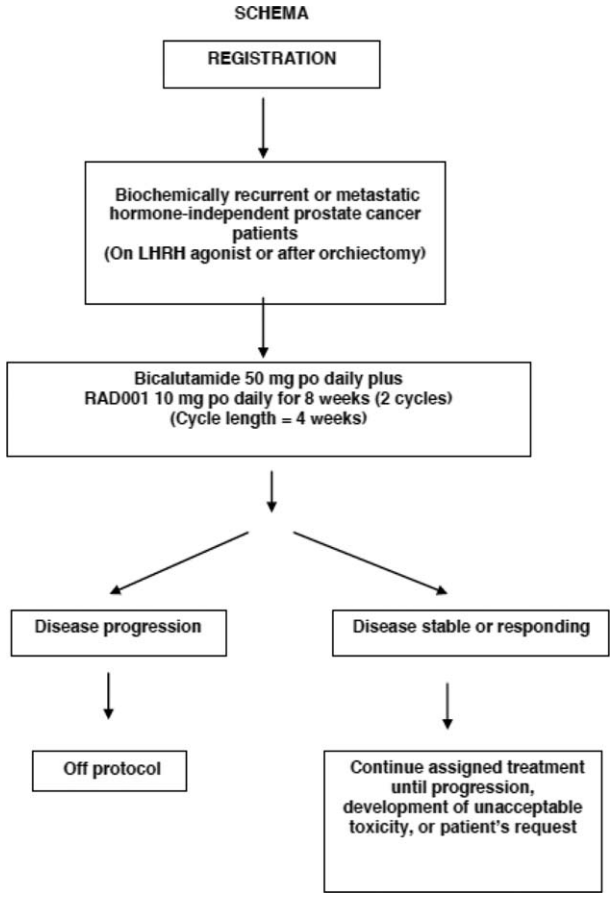

Figure 1. The clinical trial schema is illustrated. LHRH indicates luteinizing hormone-releasing hormone; po, by mouth (per os); RAD0001, everolimus (a mammalian target of rapamycin inhibitor).

observed during the first 4 weeks, the trial entered phase 2; 8 patients who were recruited in the lead-in safety phase were included in the final efficacy analysis (Fig. 1).

Study Endpoints

The primary objective of the trial was to determine the PSA response rate of bicalutamide plus everolimus in the treatment of CRPC after first-line ADT. The PSA response rate was defined as a 30% reduction in the PSA level from baseline. A 30% reduction was selected as the principal response discriminant (instead of 50% according to the criteria of Bubley et al) because of data from the Southwest Oncology Group 9916 trial of docetaxel/estramustine versus mitoxantrone/prednisone, which demonstrated that the 30% level met the Prentice criteria for survival surrogacy.[14] However, patients who experienced a reduction $\geq$50% in PSA level, according to the Bubley et al criteria,[15,16] also were recorded in the database and included for the final analysis. Secondary objectives were to evaluate the time to treatment failure and overall survival of patients with CRPC who received treatment with bicalutamide plus everolimus and to assess the toxicity of bicalutamide and everolimus.

Efficacy Assessment and Safety Assessment

We used the PSA Working Group consensus criteria[16] combined with radiographic studies to determine the proportion of patients with a PSA decline and the time to progression. Response and progression were evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[17] PSA criteria for response and progression were based on the PSA Working Group consensus criteria.[16] PSA declines of at least 30% with no other evidence of disease progression were recorded for each cohort. We also recorded PSA responses that were at least a 50% decline. Progressive disease was defined by any of the following criteria: 1) a 25% increase in the size of all soft tissue masses and/or the appearance of new lesions, 2) the need for radiation therapy, and 3) 2 consecutively increasing PSA measurements by >50% of the nadir PSA for patients with a PSA response or by >25% of the nadir or baseline (whichever is lower) PSA for patients without a PSA response. At baseline, PSA tests; computed tomography scans of the chest, abdomen, and pelvis; bone scans; and a clinical disease assessment for palpable lesions were performed. Postbaseline imaging studies and PSA tests were performed every 8 weeks. The study used version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events for toxicity and adverse event reporting.

Statistical Analysis

All patients who received any study drugs were assessable for toxicity and disease response. In total, 24 patients were included in the analyses. The objective of the primary analysis was to calculate the PSA decrease from baseline and to determine PSA responses $\geq$30%. Sample size was determined with the hypothesis that the addition of everolimus would increase the PSA response rate from 25% with bicalutamide alone (historic control) to 50% with the bicalutamide and everolimus combination.[18] In total, 24 patients were needed with a power of 0.8 and a Type I error α of .05 (1-sided) to detect this difference. Descriptive summary values (mean, standard deviation, minimum, maximum) were completed for quantitative variables (age, PSA at baseline and follow-up, and treatments completed) along with frequency percentages for categorical variables (treatment, treatment frequency, best

response, survival status, ethnicity, race). The observed proportion, with exact 95% confidence interval (CI), was calculated for each response level: complete response, partial response, stable disease, and progressive disease. Overall survival and progression-free survival were estimated using the Kaplan-Meier method. The percentage PSA decrease from baseline was defined at each follow-up as 100% × (baseline PSA − PSA at nadir)/baseline PSA. The number and proportion of patients whose PSA decrease was ≥30% for at least 1 follow-up were calculated as the primary response, and the number of those who had a PSA decrease >50% was calculated as a secondary response. The number of adverse responses was summarized by type and severity.

RESULTS

Patient Characteristics

In total, 24 patients were recruited from February 20, 2009 to January 4, 2013 and received treatment with the bicalutamide and everolimus combination. Patients' baseline demographic data are summarized in Table 1. All treated patients were included in the assessment of efficacy and toxicity and in the survival analyses. The mean patient age was 71.1 years (range, 53.0-87.0 years), and the mean number of treatments completed was 8 cycles (range, 1-23 cycles). The mean PSA level at study entry was 43.4 ng/dL (range, 2.5-556.9 ng/dL). The maximum percentage PSA decrease was calculated as the baseline PSA value minus the nadir PSA value divided by the baseline PSA value. On average, the patients had received 2.7 years (range, 1-6 years) of ADT before entering the clinical trial. Bone and lymph nodes were the most frequent sites of metastasis. Fourteen patients had bone metastases, and 3 had lymph node involvement only (58% and 13%, respectively). Three patients had both bone and lymph node metastases (13%). Two patients (8%) had nonmetastatic CRPC with biochemically recurrence only. Furthermore, only 1 patient (4%) had received 1 previous chemotherapeutic regimen with docetaxel-based chemotherapy. It should be noted that 20 of 24 patients (83%) received further treatments (hormone and/or chemotherapy) after disease progression; 5 patients (21%) received ≥2 lines of a chemotherapy regimen, and 16 (67%) received further hormone manipulation. At the time of data collection cutoff on July 31, 2013, 4 patients (17%) ultimately had progressive disease, 2 (8%) were removed from the trial because of excessive toxicities, 1 (4%) was removed because of unrelated renal artery stenosis, 5 (21%) decided to withdraw from the study, 2 (8%) died from causes other than CRPC, and 3 (12%) were still receiving treatment. Among these patients, 87% were of Caucasian descent, 4% were Asian, and 8% were African American.

TABLE 1. Patient Characteristics

Characteristic, N = 24	No. of Patients (%)
Age: Mean [range], y	71.1 [53–87]
Treatment completed: Mean no. of cycles [range]	7.9 [1–23]
PSA level: Mean [range], ng/mL	43.4 [2.5–556.9]
Race	
Caucasian	20 (87.5)
African American	3 (8.33)
Asian	1 (4.17)
Gleason score	
<7	1 (4)
7–10	21 (88)
Not available	2 (8)
Site of disease: Before treatment	
Bone	14 (58)
Lymph nodes	3 (13)
Bones and lymph nodes	3 (13)
PSA only	2 (8)
Bladder	1 (4)
Liver	1 (4)
Prior chemotherapy	
1 Line, docetaxel	1 (4)
≥2 Lines	0 (0)

Abbreviation: PSA, prostate-specific antigen.

Efficacy

First, we determined the PSA response. Of 24 patients, 18 (75%; 95% CI, 0.53-0.90) had a maximum PSA decrease ≥30% according to the proposed study protocol (Fig. 2). The range of response duration for these 18 patients was from 0 to 21.6 months (median, 5.6 months) compared with 3.2 months in a reported historic cohort that received bicalutamide alone.[19] Of these 18 patients, the duration for the 30% PSA drop ranged from 0.3 to 34 months; the earliest starting time was at 0.3 months after baseline. Of the 24 patients, 15 (62.5%; 95% CI, 0.41-0.81) had PSA decrease ≥50%.

In addition to the PSA response, we also evaluated the response according to RECIST criteria (Table 2). Of all 24 patients, 1 (4%) had a complete response (95% CI, 0.1%-21%), 4 (17%) had a partial response (95% CI, 5%-37%), 14 (58%) had stable disease (95% CI, 37%-78%), 4 (17%) had progressive disease (95% CI, 5%-37%), and 1 (4%) had missing values (Table 2).

For updated survival status with data cutoff on February 2015, 11 patients (46%) were still alive, and 13 (54%) had died. Two patients died of other causes, and 11 died of progressive disease. The Kaplan-Meier curve (Fig. 3, top) reveals that the median overall survival was

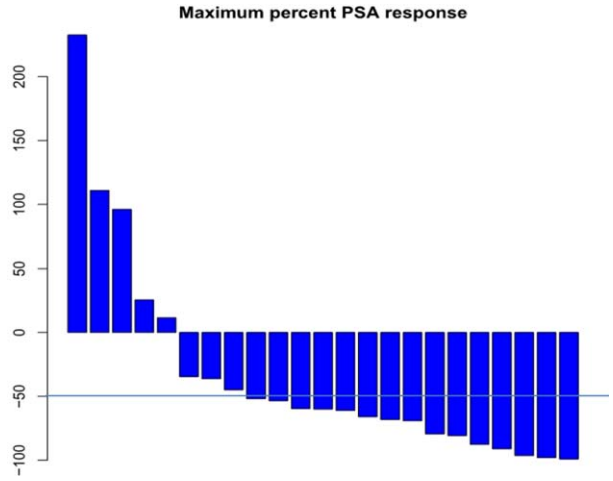

Figure 2. This is a waterfall plot of prostate-specific antigen(-PSA) response for all patients. Of 24 patients who were treated on the study, 18 patients (75%; 95% confidence interval, 0.53-0.90) had a maximum PSA decrease ≥30%, and 15 (62.5%; 95% confidence interval, 0.41-0.81) had a PSA decrease ≥50% (only 23 patients plotted as 1 patient did not have 2 time-point PSA values before disenrollment from the trial).

28 months (95% CI, 14.1-42.7 months), and the median progression-free survival was 9.4 months (95% CI, 4.0-25.0 months) (Fig. 3, bottom) compared with 5.8 months for bicalutamide alone in the historic cohort.[18]

Two patients (8%) did not have measurable disease except for rising PSA values at study entry and did not have follow-up imaging studies as specified by the protocol. On the basis of the protocol, progression-free survival was defined as the time between registration and disease progression or death that included PSA progression. Therefore, both patients were included in the final progression-free survival analysis. Five patients had early withdrawal from the clinical trial: 1 withdrew the consent form, 1 declined follow-up imaging, 1 died from narcotic overdose, and 1 was lost to follow-up and had an aortic aneurysm repair, resulting in automatic withdrawal from the study.

Toxicities

All patients who received treatment were evaluated for toxic effects. All observed toxicities are summarized in Table 3. Thirteen of 24 patients (54.2%; 95% CI, 0.328-0.745) had grade 3 toxicity, and 1 of 24 (4.2%; 95% CI, 0.001-0.211) had grade 4 toxicity. Two patients discontinued treatment secondary to toxicity. Most hematologic toxicities were mild, with 1 episode of grade 3 neutropenia, 2 episodes of grade 3 anemia, and 1 episode of grade 3 thrombocytopenia. Two patients developed grade 3 lymphopenia while on treatment. One patient had grade 4 nonneutropenic sepsis, and 1 had nonneutropenic grade 3 pneumonia.

TABLE 2. Response According to Response Evaluation Criteria in Solid Tumors

Best Response	No. of Patients	Rate (95% CI), %	Combined Rate, %
Response			20.8
CR	1	4.2 (0.1–21.1)	
PR	4	16.7 (4.7–37.4)	
SD	14	58.3 (36.6–77.9)	58.3
PD	4	16.7 (4.7–37.4)	16.7
NA	1	4.2 (0.1–21.1)	4.2

Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; NA, not available; PD, progressive disease; SD, stable disease.

Of the nonhematologic toxicities (Table 3), the most common adverse events were grade 3 oral mucositis (4 patients) and hyperglycemia (2 patients). These symptoms improved after an everolimus dose reduction. Other significant toxicity included 1 patient with grade 3 pneumonitis attributed to everolimus and another with a grade 3 thromboembolic incident.

We also investigated the association between grade ≥2 hyperglycemia, hypertriglyceridemia, and hypercholesterolemia and PSA and RECIST response. The Fisher exact test indicated that there was no association between those grade ≥2 toxicities in terms of a PSA response of 30% or 50% ($P = 1.0$) because of the small sample size of 7 patients. According to RECIST criteria, all 5 patients who had grade 2 or 3 hyperglycemia achieved stable disease. There was 1 patient each with grade 2 hypertriglyceridemia and grade 2 hypercholesteremia.

DISCUSSION

This single-institution, single-arm, phase 2 study with a lead-in safety phase was conducted to assess the efficacy and tolerability of everolimus combined with bicalutamide in 24 men who had CRPC. The trial indicated encouraging clinical activity, with a PSA response (a decrease ≥30%) observed in 75% patients who received the combination therapy of an AR agent (bicalutamide) and an mTOR inhibitor (everolimus). However, this regimen also was associated with significant toxicity: 14 of 24 patients (58.3%) experienced grade 3 or 4 toxicity.

The results of this study contrast with what was reported in an earlier clinical trial by Nakabayashi et al,[20] who observed that adding everolimus for disease that was resistant to bicalutamide was ineffective in patients with CRPC. The major difference between these 2 trials is that 31 patients (86%) in the earlier trial had previously received treatment with bicalutamide for a median duration of 7.4

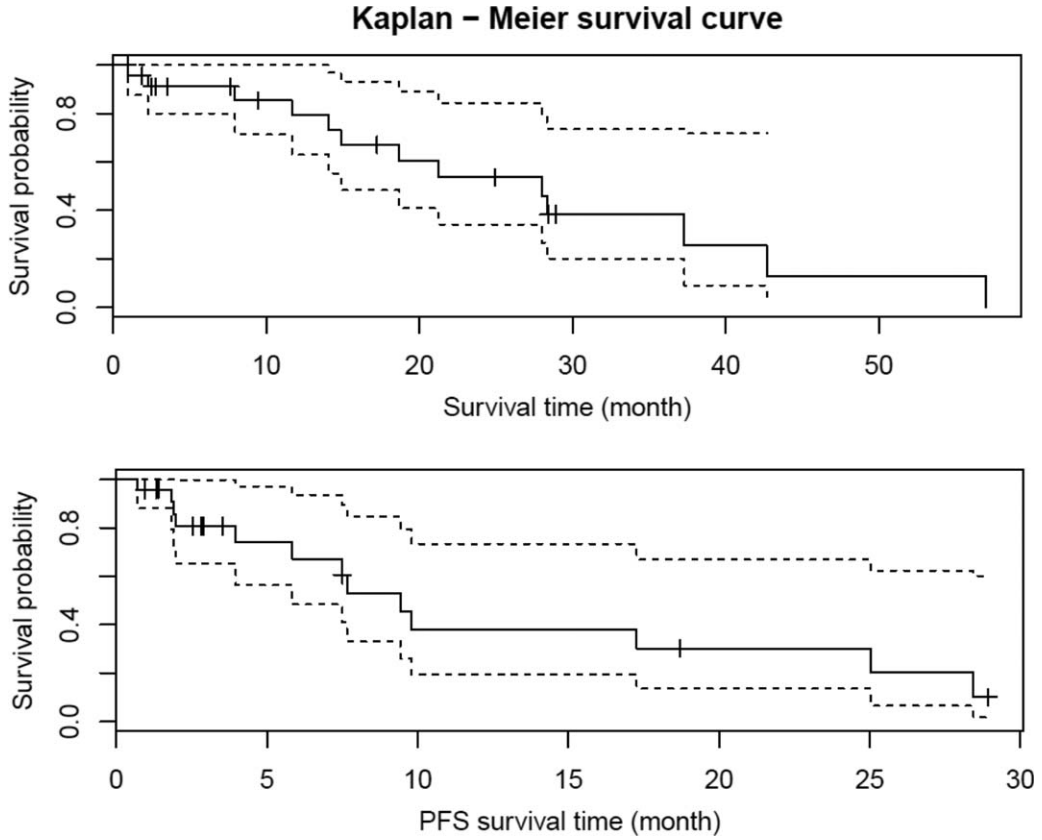

Figure 3. (*Top*) Overall survival and (*bottom*) progression-free survival are illustrated for all patients. PSA indicates prostate-specific antigen.

months when everolimus was added.[20] The response rate to bicalutamide alone in patients with CRPC was <25%, and the duration of response to bicalutamide was 3.1 months.[19] Therefore, in the trial by Nakabayshi et al, by the time everolimus was added, almost all patients had already developed resistance to bicalutamide. In other words, functionally, in their clinical trial, the treatment was equivalent to inhibiting the mTOR pathway as a single modality. Considering our previous findings that inhibition of the mTOR pathway up-regulated the AR pathway and PSA production, it was not surprising that only 2 of 36 patients had a PSA response ≥50%. A more recent study reported a PSA response rate (a 50% decrease from baseline) of 56.9% with bicalutamide alone for patients with nonmetastatic CRPC.[21] Only 2 patients (8%) in our population had nonmetastatic CRPC. Therefore, the response rate of our patients should be closer to that of the historic control cohort (25%).[3,5]

The response rate observed in the current study was comparable to that observed with newer agents targeting the androgen signaling pathway. In a study with abiraterone in patients with chemotherapy-naive CRPC, a PSA reduction ≥50% from baseline was observed in 62% of patients.[22] In another study with enzalutamide in a similar population of chemotherapy-naive patients with CRPC, a PSA decline ≥50% from baseline was observed in 78% of patients.[23] However, despite the addition of enzalutamide to the repertoire of treatment for CRPC, the drug was not yet available in much of the world; and, because of cost, it may not be available to many patients. Therefore, this bicalutamide and everolimus combination would be a potentially cost-effective option.

One major strength of this bench-to-bedside clinical trial is the design, which was based on our previous, strong preclinical studies. Everolimus is a novel oral derivative of rapamycin. At the cellular and molecular levels, mTOR is a key and highly conservative serine-threonine kinase; it is present in all cells and is a central regulator of protein synthesis and, ultimately, cell growth, cell proliferation, angiogenesis, and cell survival. Studies in both cancer cell lines and animal models have demonstrated that treatment with rapamycin delays but does not completely prevent tumor growth.[24,25] Incomplete growth inhibition with rapamycin is because of the stimulation of AR expression and transcriptional activity

TABLE 3. All Grade Toxicities for All Patients Treated With the Everolimus and Bicalutamide Combination

	No. of Patients		
Toxicity	All Grades	Grade 3	Grade 4
Anemia	14	2	0
Acne	1	0	0
ALT increased	4	0	0
ALK phosphatase increased	6	0	0
Anal mucositis	1	0	0
Anorexia	5	1	0
Abdominal pain	3	1	0
AST increased	8	0	0
Constipation	3	0	0
Constitutional symptoms	1	0	0
Diarrhea	4	0	0
Dry mouth	1	0	0
Dry skin	2	0	0
Dyspnea	3	0	0
DVT/PE	0	1	0
Edema	6	0	0
Fatigue	13	0	0
Hand-foot syndrome	1	0	0
Hypercholesterolemia	15	0	0
Hyperglycemia	12	2	0
Hypertriglyceridemia	13	0	0
Leukopenia	17	2	0
Lymphopenia	16	3	0
Oral mucositis	14	4	0
Neutropenia	9	1	0
Nausea	1	1	0
Pneumonitis	6	1	0
Pneumonia	1	1	0
Proteinuria	3	0	0
Pruritus	2	0	0
Rash	5	0	0
Right hip pain	1	1	0
Renal failure	2	1	0
Taste alteration	4	0	0
Thrombocytopenia	8	1	0
Sepsis	0	0	1
Weight loss	2	0	0

Abbreviations: ALK, alkaline; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DVT, deep vein thrombosis; PE, pulmonary embolism.

in CaP cells lines.[26] Rapamycin-induced AR transcriptional activity promotes cell growth in CaP, and inhibition of this activity prevents the recurrence of cell growth observed in the presence of rapamycin. This activity is observed in both androgen-dependent and androgen-independent sublines of CaP cells, although bicalutamide has no effect on the growth of CRPC cells as a single agent.

Although this clinical trial demonstrated promising clinical activity, the protocol was also associated with significant toxicity. Fifty-eight percent (14 of 24 patients) developed grade 3 or 4 toxicity. Most of these toxicities were attributed to everolimus, because the patients improved after an everolimus dose reduction or temporary withholding of everolimus. Although the toxicity profile of everolimus in this study is similar to that reported in the treatment of patients with kidney cancer, more patients develop grade 3 and 4 toxicities (58.3% vs 19%).[27] One possible explanation is that more patients at an advanced age were recruited for this study. The median age of patients in this study was 71.1 years (range, 53.0-87.0 years), compared with 61 years in the kidney cancer trial. Another possibility is that ADT and antiandrogen receptor therapy sensitize patients to everolimus. A third possibility is that bicalutamide has changed the drug metabolism of everolimus. Both bicalutamide and everolimus are metabolized by cytochrome P450 3A4 (CYP3A4), and competitive inhibition can occur when the 2 drugs are combined.[28]

Increases in serum glucose, triglycerides, and cholesterol at toxicity grade $\geq$2 have been associated with response and outcome in other cancers.[29-31] These changes were considered a pharmacodynamics measure for mTOR pathway inhibition and might have potential implications for vascular risk in these patients. In our study, there were too few patients in each category to draw any conclusion about the correlation between responses to grade $\geq$2 hypercholesterolemia, hypertriglyceridemia, and hyperglycemia. With this limited number of patients, further analysis may not yield any meaningful conclusion.

Like most phase 2 clinical trials, 1 major limitation of this study is its small sample size. Hence, any random events can dramatically change the final response rate. However, the patient number was decided based on the preclinical data and historic controls. All patients were enrolled based on eligibility criteria to avoid selection bias. Even with this small number of participants, the response data suggest that this combination is indeed effective in CRPC.

In summary, combination therapy with everolimus and bicalutamide represents a promising new area of treatment for patients with bicalutamide-naive CRPC. A randomized phase 3 trial with everolimus in combination with antiandrogen therapy in CRPC is warranted. However, because of significant toxicity, modification of the study design is needed. One option is to reduce the everolimus dose, because toxicity improved in the vast majority of patients after the everolimus dose, but not the bicalutamide dose, was reduced. Because newer antiandrogen therapies with abiraterone and enzalutamide are more effective than bicalutamide in CRPC, a modified clinical trial design with everolimus in combination with abiraterone or enzalutamide can also be considered.

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CONFLICT OF INTEREST DISCLOSURES

Chong-Xian Pan is on the Novartis Pharmaceuticals Advisory Board.

AUTHOR CONTRIBUTIONS

Helen Chow: Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, and project administration. **Paramita M. Ghosh:** Conceptualization, validation, writing–review and editing, and funding acquisition. **Ralph deVere White:** Conceptualization, resources, data curation, writing–review and editing, and supervision. **Christopher P. Evans:** Conceptualization, resources, data curation, writing–review and editing, and supervision. **Marc A. Dall'Era:** Conceptualization, data curation, writing–review and editing, and supervision. **Stanley A. Yap:** Resources and writing–review and editing. **Yueju Li:** Formal analysis. **Laurel A. Beckett:** Validation, formal analysis, data curation, writing–review and editing, and visualization. **Primo N. Lara, Jr:** Conceptualization, methodology, investigation, resources, data curation, writing–review and editing, and supervision. **Chong-Xian Pan:** Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, and project administration.

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