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PHASE II STUDIES

Randomized phase II trial of neoadjuvant everolimus in patients with high-risk localized prostate cancer

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Summary

Background Despite definitive local therapy, patients with high-risk prostate cancer have a significant risk for local and distant failure. To date, no systemic therapy given prior to surgery has been shown to improve outcomes. The phosphatidilinositol 3-kinase/AKT/mTOR pathway is commonly dysregulated in men with prostate cancer. We sought to determine the clinical efficacy and safety of the mTOR/TORC1 inhibitor everolimus in men with high-risk prostate cancer undergoing radical prostatectomy. *Methods* This is a randomized phase II study of everolimus at two different doses (5 and 10 mg daily) given orally for 8 weeks before radical prostatectomy in men with high-risk prostate cancer. The primary endpoint was the pathologic response (histologic P0, margin status, extraprostatic extension) and surgical outcomes. Secondary endpoints included changes in serum PSA level and treatment effects on levels of expression of mTOR, p4EBP1, pS6 and pAKT. *Results* Seventeen patients were enrolled: nine at 10 mg dose and eight at 5 mg dose. No pathologic complete responses were observed and the majority of patients (88%) had an increase in their PSA values leading to this study being terminated early due to lack of clinical efficacy. Treatment-related adverse events were similar to those previously reported with the use of everolimus in other solid tumors and no additional surgical complications were observed. A significant decrease in the expression of p4EBP1 was noted in prostatectomy samples following treatment. *Conclusions* Neoadjuvant everolimus given at 5 mg or 10 mg daily for 8 weeks prior to radical prostatectomy did not impact pathologic responses and surgical outcomes of patients with high-risk prostate cancer. **Trial registration** NCT00526591.

Keywords Prostate cancer · Neoadjuvant · Radical prostatectomy · Prostate-specific antigen (PSA) · mTOR inhibitors · Everolimus

Introduction

High-risk prostate cancer (PCa), defined by unfavorable pre-treatment features (PSA ≥ 10 ng/ml, Gleason sum ≥7, or clinical stage ≥ T2b), is a heterogeneous disease frequently managed with either radical prostatectomy (RP) or external beam radiotherapy (EBRT) in combination with long-term androgen deprivation therapy. In spite of this, a significant number of patients undergoing local definitive therapy have a significant risk of disease progression and ultimately death [1–3]. A major area of prostate cancer research has focused on the evaluation of systemic therapies given prior to or after local definitive treatments with the potential of improving clinical outcomes.

Although a multidisciplinary approach is the standard of care when managing high-risk PCa [3], to date no systemic therapy given prior to surgery has shown improved outcomes in this patient population. Multiple trials evaluating neoadjuvant ADT and chemotherapy prior to RP have failed to show pathological downstaging. These treatments do not appear to delay time to biochemical recurrence (BCR), time to clinical metastases or time to death [4–11].

The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is a pivotal oncogenic signaling pathway that has been linked to tumor progression

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in a wide variety of solid tumors including PCa [12, 13]. Multiple genomic alterations of the PI3K/AKT/mTOR pathway including PTEN and AKT loss have been associated with BCR after RP, shorter time to metastases and resistance to chemotherapy in castration-resistant prostate cancer (CRPC) [14–21]. Several agents capable of blocking mTOR signaling have been approved by the United States Food and Drug Administration (FDA) and their use is now considered standard of care in multiple other solid tumors [22–25].

Everolimus, an oral derivative of rapamycin, inhibits mTOR/TORC1, a protein kinase downstream of PI3K and Akt, involved in the regulation of cell growth, proliferation and survival. In preclinical models, the administration of everolimus was associated with reduction of mTOR downstream phosphorylated (p)-S6 (p-S6) and p-4E-BP1, and occasionally with increase in upstream p-Akt. Early studies on androgen-independent prostate cancer lines (LNCaP) treated with everolimus showed promising results with reduction in tumor volume in mice as well as decrease in serum PSA by up to 68% [26]. From these findings it was postulated that agents such as rapamycin and everolimus given prior to surgery can lead to inhibition of p-S6 in prostate cancer tissue. However, the relationship of this finding to clinical outcomes in PCa patients remains unknown [27–29]. In an effort to assess the potential efficacy and safety of everolimus in the neoadjuvant setting and to correlate its clinical efficacy with biologic endpoints, we conducted a neoadjuvant study of everolimus in high-risk PCa patients who were scheduled to undergo RP.

Patient and methods

Patient inclusion criteria and treatment protocol

Patients were enrolled in this study between July 2008 and April 2011. The Cleveland Clinic Institutional Review Board reviewed and approved the trial in accordance with an assurance filed with and approved by the Department of Health and Human Services. Eligibility criteria included histologically documented, high-risk localized PCa. This was defined by a serum PSA level of ≥10 ng/mL (any grade or stage); clinical Stage T2b, T2c, or T3 (any PSA level or grade); biopsy Gleason sum of 7 (4 + 3 only) or ≥ 8 with any stage or PSA level; or any stage/PSA/Gleason patients with a 35% or greater chance of biochemical failure at 5 years based on Kattan's nomogram [30]. Clinical stage was assigned on the basis of the digital rectal examination (DRE) findings, according to the 1997 American Joint Committee on Cancer criteria [31]. All patients were candidates for RP with available tissue from their diagnostic TRUS/biopsy, had no evidence of metastatic disease and had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Adequate renal, hepatic and bone marrow function within 8 weeks of study entry was required as defined by serum creatinine and liver function tests (AST/ALT and bilirubin) ≤ 1.5 x upper limit of normal, ANC ≥ 1500 μL, hemoglobin ≥8 mg/dL and platelets ≥100,000/μl.

Exclusion criteria included pure neuroendocrine or small cell histology, prior hormonal therapy (except previous use of 5-α reductase inhibitor for chemoprevention), steroid use, prior radiation or cytotoxic therapy and any malignancy other than basal cell carcinoma of the skin within 5 years of study entry. The pre-treatment evaluation included medical history and physical examination, complete blood count, serum chemistry panel, testosterone and PSA measurements. Patients were required to have a full body bone scan, and computed tomography or magnetic resonance imaging of the abdomen and pelvis. During the conduct of the study the protocol was amended to require a detailed assessment of the medical history of Hepatitis B and C which was done at screening as per everolimus label. HBV DNA and HCV RNA PCR testing were required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection.

Treatment consisted of everolimus administered orally once daily for 8 weeks. A web-based randomization system was used to assign patients in a 1:1 ratio to receive everolimus high dose (10 mg) or low dose (5 mg). No dose escalation was offered to either of the two dose cohorts. PSA values were collected at baseline and at week 4 and 8 post-treatment with everolimus. Patients were required to have adequate ANC (≥1500/μl) and platelet count ≥100,000/μl before proceeding with the treatment. Dose modifications due to adverse events were permitted. Toxicity was assessed using the NIH-NCI Common terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0).

Radical prostatectomy and bilateral pelvic lymph node dissection were performed at the completion of 8 weeks of neoadjuvant everolimus treatment. RP had to be performed within 7 days of completing the last dose of everolimus. Surgery was performed according to standardized open or minimally invasive techniques. Resection of both neurovascular bundles was performed at the discretion of the surgeon. Standard postoperative management was provided as previously described [32].

Pre-treatment and post-treatment tissue specimens (diagnostic biopsies and RP surgical pathology) were assessed by central review of a single pathologist (CMG). The histologic analysis included evidence of residual cancer, necrosis, atrophy, extra prostatic extension (EPE), seminal vesicle invasion, lymph nodes and margin status. EPE was defined as evidence of prostate cancer in the periprostatic adipose tissue, and positive margins were defined as tumor touching ink. A pathologic complete response was defined as complete eradication of tumor. Pathologic down-staging was defined as evidence of decreased pathologic stage or Gleason score when compared with pre-treatment clinical stage. Postoperatively, patients were followed up with PSA determination at 6 weeks after

surgery and every 3 months thereafter. Biochemical recurrence (BCR) was defined as a serum PSA ≥ 0.2 ng/mL obtained on two different occasions at least 1 week apart. Additional therapy at the time of biochemical or clinical relapse was at the discretion of the treating physician.

Immuno-histochemical staining

For immunohistochemical analyses, samples from the diagnostic prostate biopsy cores as well as radical prostatectomy specimens were analyzed. Sections were deparaffinized. Endogenous peroxidase blocking was followed by antigen retrieval in sodium citrate (pH = 6) buffer in a microwave oven. Incubation with primary antibody was done after peroxidase blocking. Slides were incubated overnight at 4 °C with mTOR, p-4E-BP1, p-S6 (Ser235/236) and phospho-AKT antibodies (CellSignaling).

Primary antibodies were identified by ABC Detection System, visualized by DAB and counterstained with Hematoxylin. Immunostaining was evaluated by a trained genitourinary pathologist with Histoscore System. Immunostaining reaction intensity (negative, +1 (weak), +2 (moderate), +3 (strongly positive) were agreed upon before blind evaluation of the scores. Benign prostatic tissue showed strong intensity cytoplasmic staining in all markers except p-AKT which was moderately positive.

Statistical analysis

The primary endpoints of the study were pathologic response (histologic P0, margin status, extraprostatic extension) and surgical outcomes, designed to determine the clinical efficacy and safety of two different oral doses of everolimus administered prior to RP. Secondary endpoints included changes in serum PSA levels, and the effects of the two everolimus doses on levels of expression of mTOR, p4EBP1, pS6 and pAKT in tumor tissue.

A sample size of 15 patients per dose group was used in order to ensure with high probability that the dose with the greatest true efficacy was also the dose that resulted in the greatest observed efficacy. Assuming the difference in pathologic response between the two doses was >0.15, the probability of selecting the correct dose was >0.82. An early stopping rule was implemented if no efficacy was observed after 12 randomized patients (6 per arm). The rationale for this was that the likelihood of observing no efficacy in 12 patients was <10% if the underlying response potential of everolimus was at least 15% in both treatment arms. The time of data cut-off for analysis was June 2014. Efficacy analyses were performed in the intent-to-treat population. Exact two-sided 95% confidence intervals for the response rate of each treatment arm were calculated using a method based on the F distribution. Categorical and ordinal data, such as margin status, pathological stage and toxicity were summarized as frequency counts, proportions and 95% confidence intervals. Continuous measures were assessed in terms of both absolute and relative changes. Wilcoxon rank-sum test was used for continuous variables. Correlations between pairs of outcomes were assessed using Pearson rank correlations. A two-sided p value <0.05 was considered statistically significant without adjustment for multiple comparisons.

Results

Patient characteristics

Seventeen patients with high-risk PCa were enrolled in this study. Nine patients were randomized to the 10 mg everolimus dose and eight patients to the 5 mg dose. Four patients were excluded from tissue analysis: one patient due to progressive disease while on therapy and three patients in whom RP was aborted due to having unresectable disease at the time of surgery. Table 1 summarizes patients and disease characteristics for the 17 analyzed patients with available data.

The median testosterone value for the entire cohort was 480 ng/dL (IQR: 325–655 ng/dL). Pretreatment serum PSA level ranged from 4.8 to 104.5 ng/mL. The majority of patients (71%) had cT1 at the initial DRE. 13 patients (76%) had an initial Gleason score of ≥8. When using the pre-operative Kattan nomogram, 6 (42%) patients had a greater than 35% risk of biochemical failure at 5 years. Disposition of patients in this study is shown in Fig. 1.

Pathologic response

No pathologic complete responses were observed in this study. Of the 14 radical prostatectomy specimens available for pathologic analysis, none of the patients had organ-confined disease (pT2a or pT2b), and all of them had either extraprostatic extension (7/14) or seminal vesicle invasion (7/14). When the Gleason score from the pre-treatment biopsy was compared with the Gleason score from the post-treatment prostatectomy specimen, the prostatectomy-based Gleason score was lower in 16% of the patients.

PSA effects

The vast majority of patients (n = 15, 88%) had an increase in PSA during treatment. The overall median change was a 3.38 ng/mL increase (IQR 4.2 decrease to 58.4 ng/mL increase) that corresponds to a 33% increase (IQR 50% decrease to a 223% increase). Two patients (17%) had a decrease in PSA over the treatment period. There was no difference in the degree of PSA change between the two dose groups (p = 0.1).

Table 1 Baseline demographics and disease characteristics ($n = 17$)

Parameter	Overall ($n = 17$)	High dose (10 mg) ($n = 9$)	Low Dose (5 mg) ($n = 8$)	p value
Age	59 (46–68)	59 (55–67)	58 (46–68)	0.5
ECOG 0	17 (100%)	9 (100%)	8 (100%)	1
Race (Caucasian)	16/17 (94%)			
Median Baseline PSA (ng/mL)	10.6 (4.8–104.5)			
Clinical Stage				
cT1c	12 (71%)	5 (56%)	7 (88%)	
cT2-T3	5 (29%)	4 (44%)	1 (13%)	0.29
Biopsy Gleason Score				
7 (4 + 3)	4 (24%)	2 (22%)	2 (25%)	
8–10	13 (76%)	7 (77%)	6 (76%)	0.97
Baseline AUA Symptom Score				
Mild (1–7)	8 (47%)	5 (56%)	3 (38%)	
Moderate (9–19)	6 (35%)	2 (22%)	4 (50%)	
Severe (20–35)	3 (18%)	2 (22%)	1 (13%)	0.82
Pathologic Stage				
pT3a	7(40%)	3 (33%)	4 (50%)	
pT3b	7(40%)	3 (33%)	3 (38%)	
Specimen Gleason score				
3 + 4	1(10%)			
4 + 3	3 (20%)			
8–10	10 (60%)			
NA	1 (10%)			
Positive Surgical Margins	5 (30%)	5 (55%)	3 (38%)	
Lymph Node positive	3 (20%)			

Three patients enrolled and treated in this study did not undergo radical prostatectomy: one patient had progression of disease while receiving everolimus treatment (patient was started on ADT), the other 2 patients had evidence of advanced disease with grossly positive LNs at surgery (one patient was treated with brachytherapy and ADT for 6 months, one patient with EBRT and ADT). Nadir PSA after surgery was undetectable in 11 of 14 patients. Three patients had detectable postoperative PSA; one patient got ADT (PSA postop was 1 ng/mL), and the other 2 patients got adjuvant EBRT. Overall, the median follow-up was 27.7 months (IQR: 3.5–55.6).

At the time of data cut-off, 10 patients (71%) developed progressive disease (defined as 2 consecutive PSA rises after a nadir of <0.03 ng/mL). Among these, 6 patients had received low-dose everolimus (5 mg) on study. Of the ten patients with progressive disease, 8 patients (80%) received salvage EBRT and two patients started ADT. The choice of salvage treatment was left to the discretion of the treating physician. Using PSA,

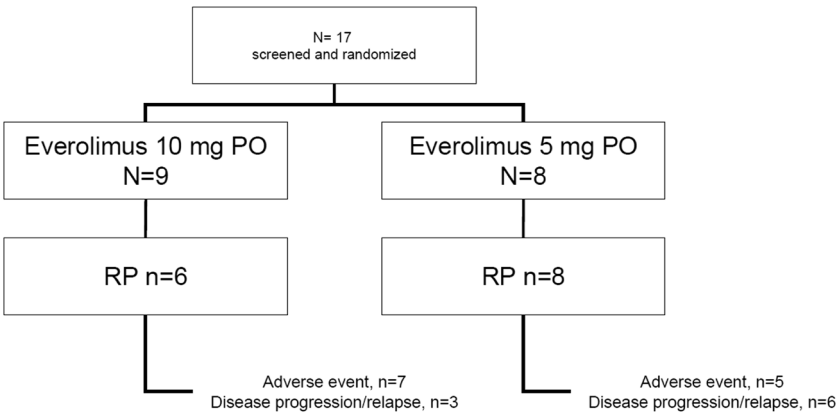

Fig. 1 Consort diagram of patient disposition in the study

the median PFS was 6 months (including 2 patients that got adjuvant RT due to a high PSA nadir post-operatively). All patients who developed disease progression had this happen within 24 months from the time of surgery. One patient died 4 years from the time of surgery from metastatic castrate resistant prostate cancer.

Safety and tolerability

Overall, treatment with everolimus was well tolerated. All patients enrolled on study received the full 8 weeks of therapy as planned. None of the patients discontinued treatment secondary to drug intolerance and no dose adjustments were required during the clinical trial. As shown in Table 2, the most commonly reported adverse events (AEs) of any grade were elevated cholesterol or triglycerides (71%), rashes (65%), and mucositis (65%). There were no hematological AEs observed among patients who received the 5 mg dose, whereas the rate of hematologic AEs was 77% in the group who received the 10 mg dose. The rates of other AEs were similar among the two treatment groups. Clinical AEs were mostly grade 1 or 2 with only three grade 3 AEs reported including one G3 hypophosphatemia and one G3 thrombocytopenia in the high dose group and one G3 hypertrigliceridemia in the low dose group. No G4 or G5 AEs were reported.

Surgical outcomes

All fourteen patients who underwent RP had tumor tissue available for analysis of biologic correlates. Ten patients underwent open RP while 4 patients had a minimally invasive approach. Median number of lymph nodes removed were 10 (range 5–20). Surgical variables are depicted in Table 3. One major intraoperative complication occurred (rectal injury requiring intraoperative loop ileostomy and conversion to open surgery). This complication was not attributed to everolimus treatment. Late post-surgical events among patients in this study included urethral strictures (6.7%) that were also felt to be in-line with expected post-operative complications. Pathological analyses revealed the presence of extraprostatic extension in 50% of patients, positive margins in 30% of patients and microscopic lymph node involvement (pN1) in 20% of patients. In terms of long-term functional outcomes, after a median follow-up of 28 months (range 14.1–87.8), full continence was demonstrated in greater than 70% of men.

Everolimus related tissue effects

Tumor tissue changes induced by treatment with everolimus were assessed by immunohistochemical (IHC) analysis from TRUS prostate biopsy cores and radical prostatectomy specimens. The selection of tissue markers (mTOR, 4EBP1, pS6, pAKT) was determined based on the proposed effects of mTOR inhibition coupled with previous studies evaluating similar markers. Pre-treatment and post-treatment matched tumor specimens were only available in 10 of 14 patients who underwent RP. IHC data comparing biopsy and RP tissue specimens is summarized in Table 4. As shown in this table, no differences in tumor tissue expression between pre- and post-treatment specimens were observed for mTOR, pS6 and pAKT. For 4EBP1 a significant decrease in all evaluated patients was observed (77.5% decrease; 5.6% to 95.7%; $p = 0.002$) (Table 4a). This trend was confirmed at further analysis among 3+ staining patterns ($p = 0.002$) (Table 4b).

Table 2 Treatment-related adverse events ($n = 17$)

	High Dose ($n = 9$)				Low Dose ($n = 8$)				Overall ($n = 17$)			
Adverse Event (G)	1	2	3	Any	1	2	3	Any	1	2	3	Any
Elevated cholesterol/TG	6	1	0	7 (78%)	2	2	1	5 (62%)	8%	3	1	12 (71%)
Mucositis	2	4	0	6 (67%)	2	3	0	5 (62%)	4	7	0	11 (65%)
Dermatologic	5	2	0	7 (78%)	3	1	0	4 (50%)	8	3	0	11 (65%)
Fatigue	2	1	0	3 (33%)	4	1	0	5 (62%)	6	2	0	8 (47%)
Hypophosphatemia	0	0	1	1 (11%)	1	4	0	5 (62%)	1	4	1	6 (35%)
Hyperglycemia	1	0	0	1 (11%)	4	1	0	5 (62%)	5	1	0	6 (35%)
Elevated AST/ALT	2	0	0	2 (22%)	4	0	0	4 (50%)	6	0	0	6 (35%)
Headache	3	0	0	3 (33%)	3	0	0	3 (38%)	6	0	0	6 (35%)
Nausea	1	0	0	1 (11%)	3	0	0	3 (38%)	4	0	0	4 (24%)
Anorexia	2	0	0	2 (22%)	1	1	0	2 (25%)	3	1	0	4 (24%)
Hematologic												
Leukopenia	4	1	0	5 (56%)				0	4	1	0	5 (29%)
Thrombocytopenia	3	0	1	4 (44%)				0	3	0	1	4 (24%)
Lymphopenia	3	1	0	4 (44%)				0	3	1	0	4 (24%)
Anemia	4	0	0	4 (44%)				0	4	0	0	4 (24%)
Any Hematologic	4	2	1	7 (78%)				0				
Maximum	2	6	1	9 (100%)	1	5	2	8 (100%)	3	11	3	17 (100%)

Table 3 Surgical outcomes for radical prostatectomy patients ($n = 14$)

Variable	Value
Patients with radical prostatectomy	14
Surgery not performed	3
Surgery duration, min	180 (95–200)
Nerve sparing procedure	
Bilateral	5
Unilateral	2
Not possible	7
Intraoperative blood loss, ml	450 (50–800)
No. of transfused blood units,n	0
Complications needing intervention	
Rectal injury	1
Time to catheter removal, days	7 (5–14)
Continence (at 28 mos), no of pads, n	
0	10
>1	4
Erectile function (at 28 mos)	
Potent	1
Potent with erection aids	1
Tumescence	2
Impotence	10

Clinical outcomes and long-term follow-up

Median clinical follow-up in this study from initiation of neoadjuvant everolimus was 78 months (Range: 13 months to 125 months). At the time of last data cutoff in January 2019, among the 17 patients initially enrolled, 5 were lost to follow-up, 6 patients had no evidence of disease recurrence (3 in low dose arm, 3 in high dose arm), and 6 patients had evidence of disease progression (2 in low dose arm, 4 in high dose arm). Among patients with disease progression, 4 had documented progression to castrate resistant prostate cancer (CRPC). The remaining two patients whose disease had progressed had hormone-sensitive disease at the time of last follow-up and were being treated with combined androgen blockage (Lupron and Bicalutamide). A total of 3 patients (18%) had passed away by the time of last follow-up (1 in low dose arm, 2 in high dose arm) from causes not related to prostate cancer.

Discussion

In this randomized phase 2 study evaluating two different doses of neoadjuvant everolimus prior to radical prostatectomy neither dose impacted pathologic response rates or surgical outcomes in patients with high-risk localized prostate cancer. Despite the negative results of this trial, a number of things can still be learned from this experience. The number of patients enrolled in each arm of the study was not sufficient to conclude whether difference in dosing could facilitate surgery and its outcomes. No difference in PSA changes was observed in either treatment arm. However, 6 out of 9 patients who had disease progression after a median follow-up of 27 months, were in the low dose arm (5 mg daily). Additionally, a decrease in the post-treatment expression of p-4EBP1, a downstream marker of mTOR was detected, showing an effect of everolimus on prostate tumor tissue. Unfortunately, the trial enrollment was stopped early due to a clear lack of histologic improvement among patients in the study.

The relative clinical utility of rapalogues (rapamycin and its analogues like everolimus) has been limited and a number of hypotheses for this have been proposed. Potential reasons include the release of S6K (immediate downstream of mTORC1), IGF1R-IRS negative feedback loop, and the resulting increase in AKT activation. AKT activation has been shown to be one of the major causes of rapalogue resistance [33]. Furthermore, rapamycin and its analogues are unable to completely block 4EBP proteins (which are mTORC1 substrates) that promote

Table 4 Relevant biomarkers in the study

A. Median of Intensity scores for each of the 4 mTOR pathway markers analyzed (prostate biopsy vs radical prostatectomy).

Marker	Biopsy Score	RP Score	# pts. w/ decrease (%)	Relative change	*p* value
mTOR	230 (140–290)	220 (140–260)	7 (70%)	9.3%(−46.2–64.3)	0.250
p4EBP1	250 (180–290)	58 (10–220)	10 (100%)	77.5% (95.7–5.6)	0.002
pS6	72 (3–240)	26 (5–180)	7 (70%)	52.5% (85.4–333.3)	0.770
pAKT	15 (0–230)	25 (10–55)	5 (50%)	16.6% (91.4–2000)	0.230

B. Median of Intensity scores among 3+ staining samples for each of the 4 mTOR pathway markers analyzed (prostate biopsy vs radical prostatectomy).

Marker	Biopsy Score (+3)	RP Score (+3)	# pts. w/ decrease (%)	Absolute change	*p* value
mTOR	40 (0–90)	40 (10–70)	4 (40%)	0 (−50–50)	0.950
p4EBP1	60 (30–90)	8 (0–50)	10 (100%)	45 (85–10)	0.002
pS6	12 (0–60)	4 (1–40)	6 (60%)	6 (55–30	0.290
pAKT	0 (0–40)	0 (0–5)	3 (30%)	0 (40–5)	0.500

translation [34]. In addition, these mechanisms promote the formation of an alternative mTOR complex with RICTOR (mTORC2), which may serve to phosphorylate AKT at serine 473 in both cellular models and clinical samples [35]. A compromised negative-feedback loop in this signaling pathway may serve as an important means by which these cells can achieve proliferative independence. Moreover, disruption of such self-attenuating signaling may contribute to the development of adaptive resistance toward drugs targeting mitogenic signaling [36].

Studies have shown aberration or mutation of PTEN is seen in about 20% of prostate cancer patients undergoing prostatectomy [37]. PTEN aberration has been associated with increased response to everolimus [38]. Recent phase II trial showed longer PFS, PSA response in patients with PTEN deficient castration resistant prostate cancer who were treated with single agent everolimus [27]. The negative result of the trial presented here underscores the significance of biomarker directed selection of patients. This trial also raises the question of whether further refinement in targeting PI3K-AKT-mTOR signaling pathway with combination therapies involving AR signaling pathway in tumors with PTEN aberration would be associated with greater clinical benefit in patients with localized prostate cancer [39].

The study presented here, although having a randomized prospective clinical trial design, had a number of limitations. The sample size was small, although it is unlikely that given the limited clinical benefit seen among the first 17 included patients, a greater benefit would have been observed with a larger sample. Additionally, this study enrolled patients only at a single tertiary academic center which may limit the generalizability of observed results.

In summary, both 5 mg and 10 mg doses of everolimus administered as neoadjuvant treatment for 8 weeks to patients with high-risk prostate cancer prior to radical prostatectomy were well tolerated and did not impact peri-operative morbidity. However, there was limited clinical benefit in terms of pathologic responses and PSA changes with neoadjuvant everolimus treatment, leading to the early termination of this trial.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no specific conflicts of interest related to this manuscript. Jorge A. Garcia received Research Funding - paid to institution: Novartis and GSK.

Ethical approval All procedures performed in this study involving human participants were approved by the Cleveland Clinic Institutional Review Board. All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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