Overview

The Oncologist®
The official journal of the Society for Translational Oncology

First Published Online November 5, 2015

DOI: 10.1634/theoncologist.2015-0220

Title: Temsirolimus Maintenance Therapy After Docetaxel Induction in Castration-Resistant Prostate Cancer

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Canadian Cancer Trials Identifier: TEM Prostate (registered with http://www.canadiancancertrials.ca)

Sponsor: Pfizer (formerly Wyeth)

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IRB Approved: Yes

Disclosures

Scott Berry: Sanofi (H); **Robert S. Kerbel:** Cerulean Pharma, MolMed, Merrimack (C/A), Triphase Accelerator (C/A, RF), Angiocrine Biosciences (C/A, OI), Eli Lilly, Boehringer Ingelheim (C/A, H); **Eric Winquist:** Imclone Systems, Exelixis, Oncogenex, Roche/Genetech (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Lessons Learned

Temsirolimus maintenance therapy after docetaxel induction chemotherapy

- is safe in patients with castration-resistant prostate cancer, although biochemical or tumor responses are rare;
- does not diminish quality of life; and
- delays radiological and/or symptomatic progression by approximately 6 months.

Author Summary: Abstract and Brief Discussion

Background

No standard therapy is available for men with castration-resistant prostate cancer (CRPC) who have responded to docetaxel and do not yet have disease progression. Hence, we designed a single-arm phase II trial to explore whether the mTOR inhibitor temsirolimus can maintain the response to docetaxel without compromising quality of life.

Methods

After successful docetaxel induction (75 mg/m^2 every 3 weeks; 6–10 cycles), 21 CRPC patients underwent temsirolimus maintenance treatment (25 mg weekly; 4 weeks per cycle). The primary endpoint was the time to treatment failure (TTTF) (i.e., radiological and/or symptomatic progression). The secondary endpoints included the tumor response rate (RECIST 1.0), safety (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0), quality of life (Functional Assessment of Cancer Therapy-Prostate [FACT-P]), pain (Present Pain Intensity [PPI] scale), prostate-specific antigen (PSA) parameters, including time to PSA progression (TTPP) according to Prostate Cancer Clinical Trials Working Group criteria, and serial enumeration of circulating endothelial cells (CECs) and endothelial progenitor cells (CEPs).

Results
Patients received a median of 7 cycles of temsirolimus (range, 1–28), resulting in a median TTTF of 24.3 weeks (95% confidence interval [CI], 16.1–33.0), 1 partial tumor response (4.8%), 1 PSA response (4.8%), and a median TTPP of 12.2 weeks (95% CI, 7.8–23.9). Grade 3–4 adverse events were infrequent, and FACT-P and PPI scores remained stable during treatment. CECs did not predict clinical benefit, and CEPs were not consistently detectable.

Conclusion
Temsirolimus maintenance therapy after successful docetaxel induction is feasible, does not adversely affect quality of life, and, in this exploratory single-arm phase II study, resulted in a median TTTF of 24.3 weeks.

Discussion
In the absence of progression or prohibitive toxicity, docetaxel chemotherapy is usually administered for up to 10 cycles for the treatment of CRCP. However, the optimal duration of docetaxel therapy has not been determined. As opposed to treating to progression or to a finite number of cycles, two different strategies have been explored in preliminary studies: (a) intermittent docetaxel chemotherapy (supplemental online Table 1); and (b) maintenance therapy using various agents (supplemental online Table 2). We present the findings of the first study of temsirolimus maintenance therapy in 21 CRPC patients after successful docetaxel induction. The rapalog mTOR inhibitor (mTORi) temsirolimus was chosen because of the high rate of PI3K-AKT-mTOR pathway abnormalities in CRPC, preclinical temsirolimus activity in various prostate cancer models, and the favorable safety profile of rapalog mTORis.

Temsirolimus maintenance therapy resulted in a median TTTF of 24.3 weeks (95% CI, 16.1–33.0) (Fig. 1A; Table 2). Biochemical progression preceded symptomatic (61.9%) and/or radiological (23.8%) progression in most patients, accounting for a TTPP of 12.2 weeks (95% CI, 7.8–23.9) (Fig. 1A, 1B; Table 2). Aside from a single PSA and a partial tumor response, we documented any PSA decline in 10 of 20 evaluable patients, and stable disease was observed in 61.9% of patients (Fig. 1C; Table 2). Grade 3 treatment-related side effects such as hyperglycemia were infrequent (9.5%), and one grade 4 thromboembolic event occurred. One patient withdrew consent because of grade 2 peripheral edema, considered "possibly" treatment related. Temsirolimus did not diminish quality of life as assessed using the FACT-P questionnaire (Fig. 2A), nor did we observe significant changes in pain (Fig. 2B) or performance status (data not shown) during treatment.

Our findings confirm the typically cytostatic effects of rapalog mTORis observed in different stages of CRPC (supplemental online Table 3), possibly due to only partial PI3K-AKT-mTOR pathway inhibition and compensatory activation of other signaling pathways. However, considering the acceptable safety profile of temsirolimus, the TTTF of 24.3 weeks compares favorably with treatment-free intervals of approximately 4–5 months observed in intermittent chemotherapy trials (supplemental online Table 1). Furthermore, maintenance temsirolimus is superior to ketoconazole or sunitinib, while similar results were achieved with granulocyte macrophage colony-stimulating factor (supplemental online Table 2).

Despite significant changes in the CRPC treatment landscape since the inception of this study in 2008, postdocetaxel maintenance strategies remain relevant. The PI3K-AKT-mTOR pathway contributes to resistance to novel androgen receptor pathway inhibitors such as abiraterone and enzalutamide. However, given the pharmacological shortcomings of rapalog mTORis, future trials might study ATP site mTORis or dual PI3K/mTORis, or select patients with genetic features predicting sustained responses to mTORis.

Trial Information

Disease	Prostate cancer
Stage of Disease/Treatment	Metastatic/advanced
Previous Therapy	More than 2 previous regimens
Type of study - 1	Phase II
Type of study - 2	Single arm
Primary Endpoint	Time to treatment failure
Secondary Endpoints	Overall response rate Safety Functional Assessment of Cancer Therapy-Prostate (FACT-P) Present Pain Intensity (PPI) index Prostate-specific antigen (PSA) response rate PSA doubling time

	Time to PSA progression (TTPP) Overall survival Analyses of circulating endothelial cells and circulating endothelial progenitor cells
Additional Details of Endpoints or Study Design	**Primary endpoint** Time to treatment failure, defined as (a) objective disease progression as per RECIST 1.0 (soft tissue disease) or modified Prostate-Specific Antigen Working Group (bone metastases) criteria (new bone lesions qualifying for progression only if symptomatic; PSA progression only not considered progression); and/or (b) cancer-related symptomatic progression, defined as new or worsening disease-related symptoms requiring the initiation of further therapy for prostate cancer treatment, or a disease-related deterioration in Eastern Cooperative Oncology Group (ECOG) performance status of two levels or higher. **Secondary endpoints** Overall response rate (RECIST 1.0); safety assessment (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0); FACT-P; PPI index; PSA response rate, PSA doubling time, TTPP; overall survival; baseline counts and on-treatment changes of total, viable, and apoptotic circulating endothelial cells and endothelial progenitor cells.
Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1 **Generic/Working name**	Temsirolimus
Trade name	Torisel
Company name	Pfizer (formerly Wyeth)
Drug type	Small molecule
Drug class	mTOR
Dose	25 mg per flat dose
Route	IV
Schedule of Administration	Temsirolimus 25 mg i.v. weekly, 4-week cycles

Patient Characteristics

Number of patients, male	21
Number of patients, female	0
Stage	Metastatic castration-resistant prostate cancer (CRPC) with confirmed PSA response in the absence of any other signs of disease progression after 6–10 cycles of first-line docetaxel chemotherapy (75 mg/m^2 every 3 weeks, 5 mg of prednisone p.o. b.i.d.).
Age	Median (range): 67 (51–82)
Number of previous systemic therapies	Median (range): 2
Performance Status: ECOG	0 — 7 1 — 14 2 — 0 3 — 0 Unknown — 0
Other	Table 1 provides additional details of the baseline demographic data and clinical characteristics.
Cancer Types or Histologic Subtypes	Adenocarcinoma of the prostate without neuroendocrine differentiation 21

Primary Assessment Method

Adenocarcinoma of the Prostate Without Neuroendocrine Differentiation

Number of patients screened	32
Number of patients enrolled	21
Number of patients evaluable for toxicity	21
Number of patients evaluated for efficacy	21
Evaluation method	RECIST 1.0
Response assessment CR	*n* = 0 (0)
Response assessment PR	*n* = 1 (4.8)
Response assessment SD	*n* = 13 (61.9)
Response assessment PD	*n* = 3 (14.3)
Response assessment OTHER	*n* = 4 (19.0)
(Median) duration assessments TTTF	24.3 weeks, 95% CI: 16.1–33.0
Kaplan-Meier time units	
Weeks	

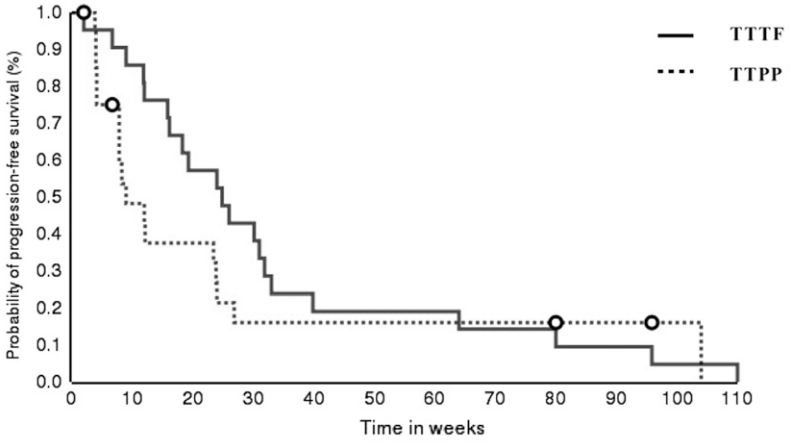
Time of scheduled assessment and/or time of event	No. with progression	No. censored	Percentage at start of evaluation period	Kaplan-Meier, %	No. at next evaluation/ No. at risk
2	1	0	100	95.24	20
6.71	1	0	95.24	90.48	19
9.00	1	0	90.48	85.71	18
11.86	1	0	85.71	80.95	17
12.00	1	0	80.95	76.19	16
15.86	1	0	76.19	71.43	15
16.14	1	0	71.43	66.67	14
18.29	1	0	66.67	61.90	13
19.29	1	0	61.90	57.14	12
24.00	1	0	57.14	52.38	11
24.86	1	0	52.38	47.62	10
26.00	1	0	47.62	42.86	9
30.14	1	0	42.86	38.10	8
31.00	1	0	38.10	33.33	7
31.86	1	0	33.33	28.57	6
33.00	1	0	28.57	23.81	5
39.86	1	0	23.81	19.05	4
64.00	1	0	19.05	14.29	3
80.00	1	0	14.29	9.52	2
95.86	1	0	9.52	4.76	1
110.00	1	0	4.76	0	0

Secondary Assessment Method

Adenocarcinoma of the Prostate Without Neuroendocrine Differentiation

Number of patients screened	32
Number of patients enrolled	21
Number of patients evaluable for toxicity	21
Number of patients evaluated for efficacy	21
Evaluation method	TTPP
Kaplan-Meier time units	
Weeks	

Time of scheduled assessment and/or time of event	No. with progression	No. censored	Percentage at start of evaluation period	Kaplan-Meier (%)	No. at next evaluation/No. at risk
2	0	1	100	100	20
3.86	1	0	100	95	19
4.00	2	0	95	85	17
4.14	2	0	85	75	15
6.71	0	1	75	75	14
7.86	3	0	75	58.93	11
8.29	1	0	58.93	53.57	10
9	1	0	53.57	48.21	9
12	1	0	48.21	42.86	8
12.14	1	0	42.86	37.50	7
23.43	1	0	37.50	32.14	6
23.86	1	0	32.14	26.79	5
24.00	1	0	26.79	21.43	4
26.86	1	0	21.43	16.07	3
80	0	1	16.07	16.07	2
95.86	0	1	16.07	16.07	1
104	1	0	16.07	0	0



No. at Risk	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1	0
	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1	0
No. censored	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0

Treatment outcomes. **(A):** The median TTTF (i.e., radiological and/or symptomatic progression) was 24.3 weeks (95% confidence interval [CI], 16.1–33), and the TTPP was 12.2 weeks (95% CI, 7.8–23.9).

Abbreviations: TTPP, time to prostate-specific antigen progression; TTTF, time to treatment failure.

Adverse Events

Adverse Events at All Dose Levels, Cycle 1

		Grade					
Name	***NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Bone pain	16%	23%	52%	9%	0%	0%	84%
Cough	44%	47%	9%	0%	0%	0%	56%
Fatigue	54%	14%	28%	4%	0%	0%	46%
Localized edema	58%	19%	23%	0%	0%	0%	42%
Anorexia	63%	19%	14%	4%	0%	0%	37%
Abdominal pain	67%	19%	14%	0%	0%	0%	33%
Weight loss	67%	14%	19%	0%	0%	0%	33%
Hyperglycemia	72%	0%	19%	9%	0%	0%	28%
Cholesterol high	72%	19%	9%	0%	0%	0%	28%
Constipation	77%	4%	19%	0%	0%	0%	23%
Hypokalemia	82%	14%	0%	4%	0%	0%	18%
Nausea	86%	14%	0%	0%	0%	0%	14%

Adverse Events Legend
*No change from baseline/no adverse event.
Summary of adverse events of any grade during temsirolimus therapy reported in >10% of patients or of grade 3 or higher if encountered in >5% of patients.

Serious Adverse Events

Name	Grade	Attribution
Biliary obstruction	3	Unlikely
Deep vein thrombosis	3	Possible
Pulmonary embolism	4	Possible
Colon cancer	4	Unrelated

Four patients presented with serious adverse events. Of note, the case of biliary obstruction was due to prostate cancer progression.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated reason	Did not fully accrue
Pharmacokinetics / Pharmacodynamics	Not collected
Investigator's Assessment	Active and should be pursued further

Discussion

Docetaxel chemotherapy is a major treatment modality of advanced CRPC. However, the optimal duration of docetaxel therapy has not been determined, although it can be associated with severe myelosuppression, neurotoxicity, cumulative asthenia, and other side effects [1]. In the TAX327 trial, CRPC patients received a median of 9.5 cycles of docetaxel (75 mg/m^2 every 3 weeks); 46% of the patients completed 10 cycles, and 38% withdrew from treatment earlier because of progression and 11% because of adverse events [1]. An exploratory analysis of the TAX327 (≤10 cycles) versus the CS-205 trial (≤17 cycles) suggested a lack of survival benefit with >10 cycles of docetaxel [2, 3]. Thus, in the absence of progression or prohibitive toxicity, in clinical practice, docetaxel is usually administered for ≤10 cycles.

As opposed to treatment to progression or to a finite number of cycles, two different strategies have been explored in preliminary CRPC studies: (a) intermittent docetaxel chemotherapy, enabling treatment-free intervals of 4–5 months in docetaxel responders (supplemental online Table 1) [4–11]; and (b) maintenance therapy using various agents (supplemental online Table 2) [12–15]. While the definite benefit of intermittent versus continuous docetaxel chemotherapy is being tested in a phase III study (ClinicalTrials.gov identifier NCT01224405), recruitment has been

suspended for a randomized, placebo-controlled phase III trial of orteronel maintenance therapy (a second-generation androgen receptor pathway inhibitor [ARi], the development of which has been terminated [16]) in CRPC patients without disease progression after docetaxel induction ($\geq$300 mg/m^2; ClinicalTrials.gov identifier NCT01707966).

We present the findings of the first prospective study of temsirolimus maintenance therapy in CRPC patients after successful docetaxel induction. Temsirolimus, an mTOR inhibitor (mTORi) of the rapalog family, was chosen because (a) PI3K-AKT-mTOR pathway abnormalities are found almost universally in CRPC [17, 18]; (b) temsirolimus was active in preclinical studies of prostate cancer models with PI3K-AKT-mTOR activation or after docetaxel chemotherapy [19, 20]; and (c) mTORis are thought to impair CRPC progression via numerous complementary mechanisms [21, 22]. Because rapalog mTORis are generally well tolerated, we hypothesized that temsirolimus would maintain the response to docetaxel without compromising quality of life [23–25].

In CRPC patients with a low disease burden after docetaxel induction (median, 6 cycles; range, 6–10; 75 mg/m^2 every 3 weeks), temsirolimus maintenance therapy (median, 7 cycles; range, 1–28; 25 mg weekly, 4 weeks per cycle) resulted in a TTTF of 24.3 weeks (95% CI, 16.1–33.0) (Fig. 1A; Tables 1 and 2). Biochemical progression preceded symptomatic (61.9%) and/or radiological (23.8%) progression in most patients, owing to a relatively short median TTPP of 12.2 weeks (range, 7.8–23.9) (Fig. 1A, B). We observed a $>$50% and an any PSA decline in 1 (5%) and 10 (50%) of 20 evaluable patients, respectively, and a partial response in 1 (4.8%) and stable disease in 13 of 21 patients (61.9%) (Fig. 1C; Table 1). Despite rarely sustained PSA control, we found significant correlations between the best PSA response and TTTF, and between TTPP and TTTF (supplemental online Fig. 1). The median overall survival of our selected group of docetaxel responders was 10 months longer than in the TAX327 study (125.1 weeks, 95% CI: 97.7 not reached) (supplemental online Fig. 2).

Temsirolimus was well tolerated, with rare grade 3 treatment-related side effects such as hyperglycemia (9.5%) and a single grade 4 thromboembolic event, and without new safety signals. One patient withdrew consent because of grade 2 peripheral edema. Temsirolimus therapy did not diminish quality of life (FACT-P questionnaire; Fig. 2A). During temsirolimus therapy, we also found no significant increases in the median PPI (Fig. 2B) or decreases in the performance status (ECOG; data not shown).

Our findings confirm the usually cytostatic effects of temsirolimus and other rapalog mTORis observed in different CRPC stages (supplemental online Table 3) [26–32]. In published series, stable disease was the best objective response in most patients, and the typically short-lived PSA declines were restricted to less than one third of patients; confirmed PSA responses were rare. Indeed, rapalog mTORis only partially block the PI3K-AKT-mTOR pathway [33]. Furthermore, mTOR inhibition activates compensatory pathways (e.g., AR and mitogen-activated protein kinase pathways) [34, 35]. In particular, compensatory AR activation might explain the low PSA response rates and short TTPP seen with mTORi monotherapy.

Considering the differences in trial design, temsirolimus appears to be superior to maintenance treatment with either ketoconazole or sunitinib in terms of efficacy (supplemental online Table 2) [14, 15] and provides a similar benefit as GM-CSF [13]. However, given the lack of a direct comparison, such conclusions must be viewed with caution. In contrast, consolidation therapy with six doses of weekly docetaxel (20 mg/m^2) and samarium-153-EDTMP after four cycles of docetaxel (70 mg/m^2) and estramustine provided a median PSA and clinical progression-free survival of 6.4 and 15 months, respectively [12].

Considering the acceptable temsirolimus side effect profile, the median TTTF of 24.3 weeks in our patients compares favorably with treatment-free intervals of 4–5 months observed in intermittent chemotherapy trials (supplemental online Table 1) [4–11]. Of note, a docetaxel rechallenge was usually triggered by PSA, rather than symptomatic or radiologic progression in the intermittent chemotherapy trials. However, in our study, we purposely focused on clinical and/or radiological progression to define treatment failure.

Given the strong antivascular effects of mTORis [22], we attempted to study the predictive potential of circulating endothelial cells (CECs) and endothelial progenitor cells (CEPs) in our patients [36]. The baseline enumeration of total, viable, and apoptotic CECs did not predict the outcome, and very low CEP counts were detectable in a few patients only (data not shown), potentially because of the low baseline tumor burden (supplemental online Fig. 3).

The CRPC treatment landscape has significantly changed since the inception of this study in 2008 [37]. However, because many future patients will have acquired resistance to second-generation ARis such as abiraterone and enzalutamide before undergoing docetaxel chemotherapy, postdocetaxel maintenance strategies remain relevant. Intriguingly, the PI3K-AKT-mTOR pathway contributes to resistance to ARis [38–40]. Thus, patients with previous ARi exposure might be particularly sensitive to

mTORis. Alternatively, concurrent mTORis might help delay resistance to ARis, similar to successful combinations of mTORis with estrogen receptor pathway inhibitors in breast cancer [41, 42]. Because of the pharmacological shortcomings of rapalog mTORis, future studies might be pursued by using ATP-site mTORis or dual PI3K/mTOR inhibitors, or by using mTORis only in patients with genetic features predicting a high rate of sustained responses [40, 43].

Acknowledgments

Urban Emmenegger expresses his gratitude to J. Bogaerts (Brussels, Belgium), P. Schöffski (Leuven, Belgium), and S.M. Swain (Washington, DC, USA) for their support with the protocol development during the Ninth FECS-AACR-ASCO workshop "Methods in Clinical Cancer Research" 2007, Flims, Switzerland. Dr. Emmenegger was supported by the Joseph and Silvana Cancer Research Fund.

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Figures and Tables

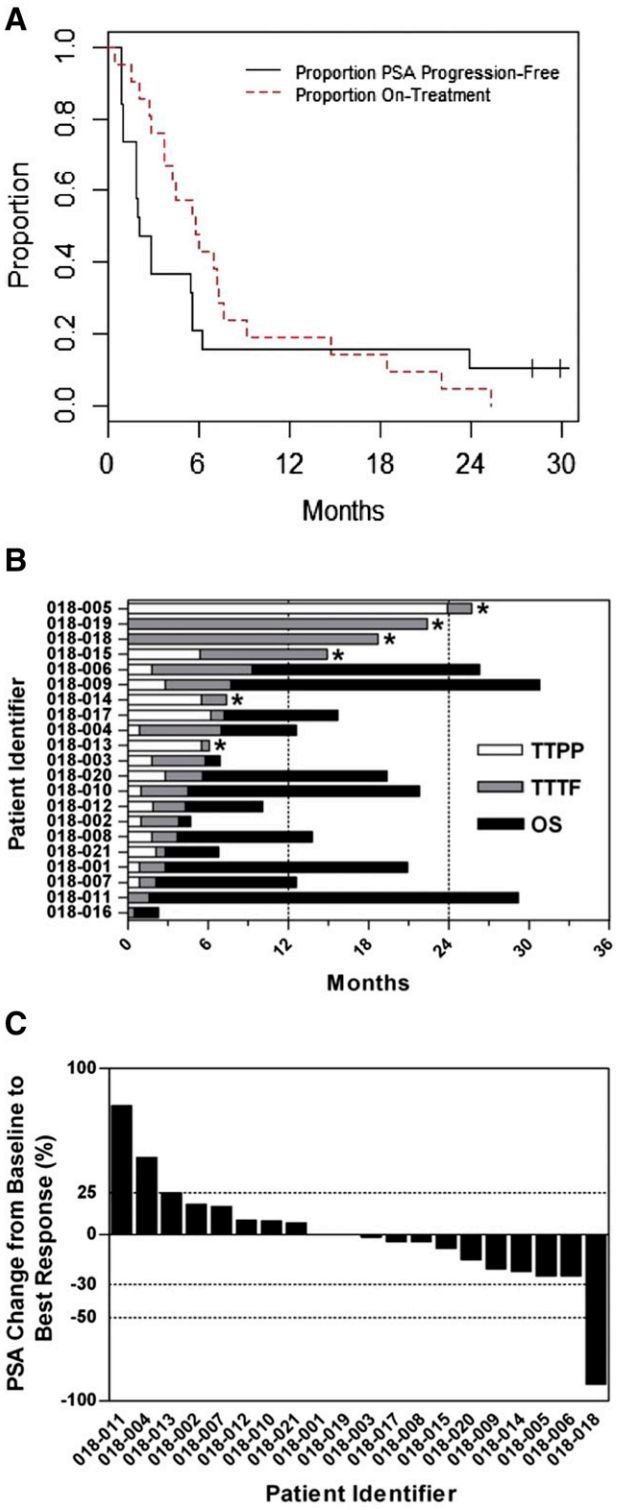


Figure 1. Treatment outcomes. **(A):** The median TTTF (i.e., radiological and/or symptomatic progression) was 24.3 weeks (95% CI, 16.1–33.0). The TTPP was 12.2 weeks (95% CI, 7.8–23.9). **(B):** Depiction of TTPP (white bars), TTTF (gray bars), and OS (black bars) in individual patients ranked according to TTTF. Asterisks indicate patients alive at study termination. **(C):** Waterfall plot of percentage of PSA changes from baseline to best response of 20 evaluable patients, revealing a PSA response >50% in 1 patient and any PSA decline in 10 patients.

Abbreviations: OS, overall survival; PSA, prostate-specific antigen; TTPP, time to PSA progression; TTTF, time to treatment failure.

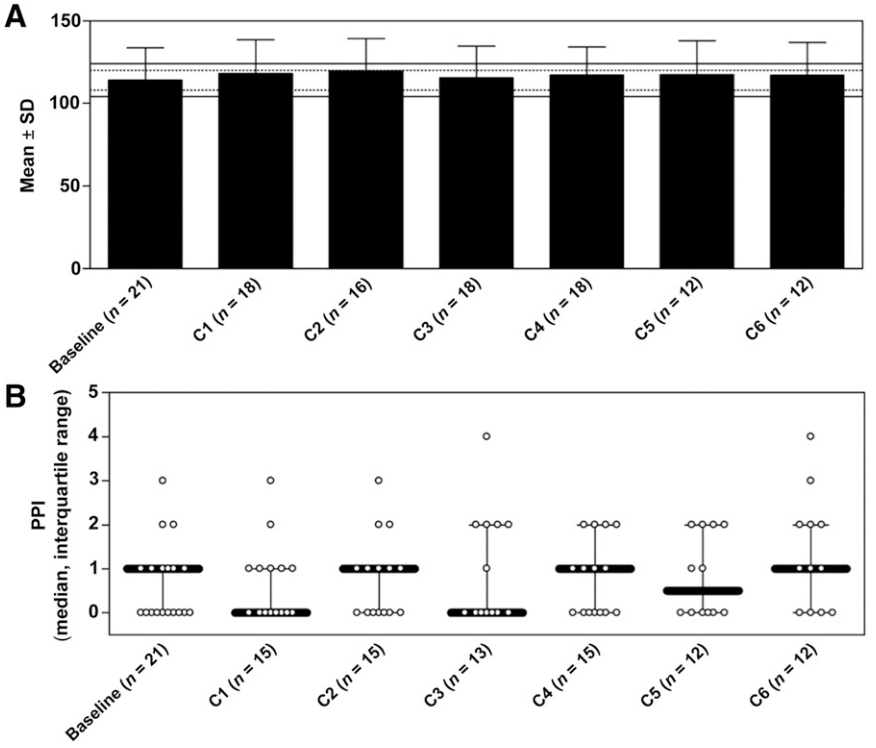
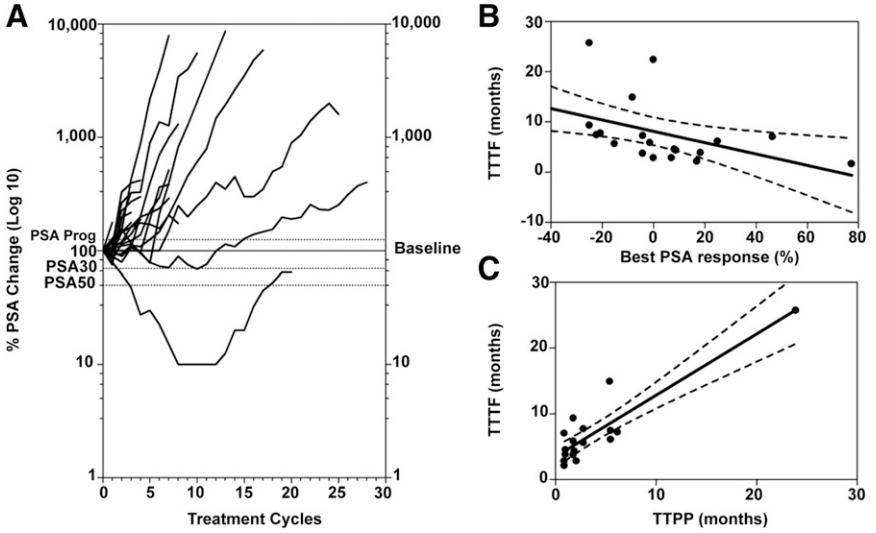


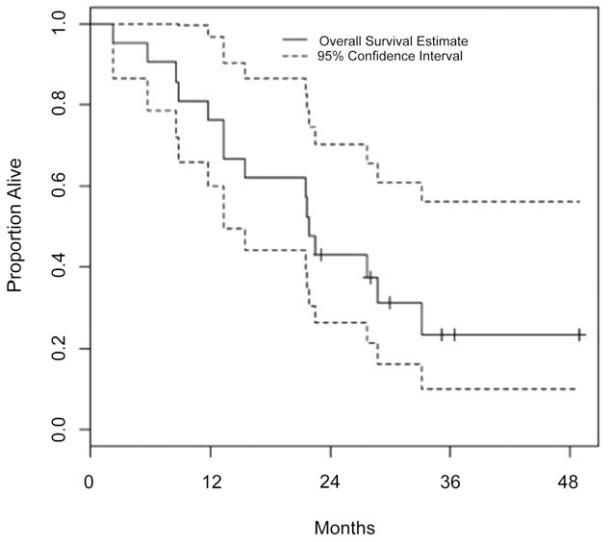
Figure 2. Quality of life and pain assessment during temsirolimus maintenance therapy. **(A):** Functional Assessment of Cancer Therapy-Prostate (FACT-P) scores were obtained at baseline and on day 1 of each treatment cycle thereafter. Compared with the mean ± SD FACT-P total score at baseline of 114 ± 19.5, no clinically meaningful changes were observed during temsirolimus maintenance therapy, using either more (broken lines) or less (continuous line) conservative minimally important difference ranges, as described by Cella et al. [44]. Also, no significant changes were seen in the FACT-P subscores (data not shown). **(B):** The median PPI score at baseline was 1 (range, 0–3) and did not significantly change during temsirolimus maintenance therapy.

Abbreviations: C, cycle; PPI, Present Pain Intensity.

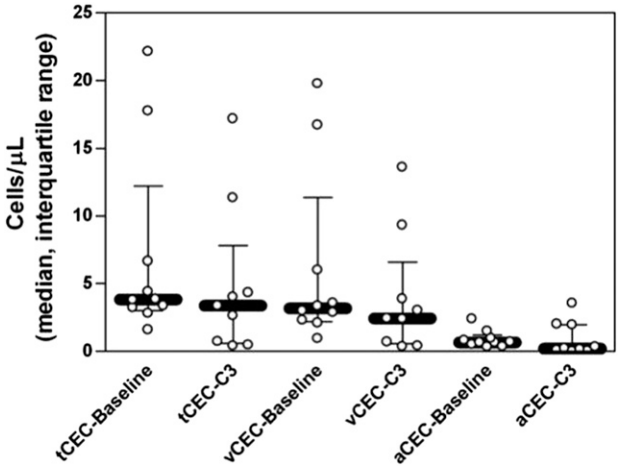


Supplemental Figure 1. Correlation of PSA parameters with time to treatment failure. **(A):** Relative PSA changes of individual patients during temsirolimus maintenance therapy. **(B, C):** TTTF correlated with the best PSA response achieved ($p = .0147$) **(B)** and with the time to PSA progression (TTPP; $p < .0001$) **(C)**.

Abbreviations: Prog, progression; PSA, prostate-specific antigen; TTTF, time to treatment failure.



Supplemental Figure 2. Overall survival analysis. The median overall survival of the study participants was 28.8 months (95% confidence interval, 22.5 - not reached).



Supplemental Figure 3. Analyses of circulating endothelial cells and circulating endothelial progenitor cells. Ten patients underwent serial analyses of circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPs) according to the method detailed by Shaked et al. [36]. There were no significant changes in tCEC, vCEC, or aCEC counts when comparing baseline values with enumerations after 3 cycles of temsirolimus. In addition, individual CEC counts did not correlate with other outcome parameters such as time to treatment failure (data not shown). Very low levels of CEPs were detectable in a small subgroup of patients only, precluding statistical analyses.

Abbreviations: aCEC, apoptotic circulating endothelial cells; tCEC, total circulating endothelial cells; vCEC, viable circulating endothelial cells.

Table 1. Baseline demographic data and clinical characteristics

Characteristic	Value
Race	
White	16
Asian	3
Black	1
Native American	1
Age (yr)	
Mean ± SD	68 ± 7.69
Median	67
Range	51–82
Gleason score[a]	
≤6	3
7	6
≥8	10
Primary local therapy	
Radiation	13
Prostatectomy	4
Prostatectomy and radiation	4
No. of lines of systemic therapy preceding docetaxel[b]	
None	1
1 Line	7
2 Lines	10
3 Lines	2
4 Lines	1
Type of systemic therapies preceding docetaxel	
Bicalutamide	20
Ketoconazole/hydrocortisone	7
Prednisone	3
Other	8
No. of docetaxel cycles	
6	10
7	2
8	8
9	0
10	1
Metastatic sites	
Bones	18
Nodes	10
Lung	6
Liver	3
PSA (μg/L)	
Mean ± SD	50 ± 92.65
Median	17.3
Range	0.02–380.7

Lactate dehydrogenase (U/L)	
Mean ± SD	227.76 ± 61.45
Median	197
Range	109–353
Alkaline phosphatase (IU/L)	
Mean ± SD	154.10 ± 148.64
Median	82
Range	44–565
Albumin (g/L)	
Mean ± SD	39.90 ± 4.45
Median	40
Range	31–47
Hemoglobin (g/L)	
Mean ± SD	118.40 ± 11.71
Median	118
Range	100–149
Present Pain Intensity score[c]	
0	10
1	7
2	2
3	1
ECOG performance status	
0	7
1	14
FACT-P total score	
Mean	114.0
SD	19.5

Data presented as *n*, unless otherwise noted.
[a]Not available for 2 patients.
[b]Excluding androgen deprivation therapy.
[c]Available for 20 patients.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; FACT-P, Functional Assessment of Cancer Therapy-Prostate; PSA, prostate-specific antigen.

Table 2. Treatment information and efficacy

Variable	Value
Total cycles	
Median	7
Range	1–28
Total temsirolimus dose (mg)	
Median	545
Range	50–2,750
Time to treatment failure (wk)	
Median	24.3
95% CI	16.1–33.0
Maximum PSA reduction (%)	
Median	0
Range	−90.0 to +18.4

Time to PSA progression (wk)	
Median	12.2
95% CI	7.8–23.9
PSA doubling time (wk)	
Median	10.9
Range	4.3–204.1
Overall survival (wk)	
Median	125.1
95% CI	97.7–NR
Best objective response	
PR	1 (4.8%)
SD	13 (61.9%)
PD	3 (14.3%)
Nonevaluable	4 (19.0%)
Reasons for treatment failure[a]	
Symptomatic progression	13 (61.9%)
Radiological progression	5 (23.8%)
Toxicity	1 (4.8%)
Intercurrent illness	1 (4.8%)
Patient withdrawal	1 (4.8%)
Investigator discretion	1 (4.8%)

Data are presented as *n* (%), unless otherwise noted.
[a]Multiple counting allowed.
Abbreviations: CI, confidence interval; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

Supplemental Table 1. Intermittent docetaxel chemotherapy for castration-resistant prostate cancer

Reference	Study type	*n*	Treatment details	Trigger for treatment interruption	PSA50	Percentage reaching first treatment-free interval	Duration of first treatment-free interval	Trigger for docetaxel rechallenge
Beer et al. 2003, 2004 [4, 5]	Single-arm phase II (substudy)	8 of 37 patients	Weekly DOC (36 mg/m^2; day 2) + weekly calcitriol (0.5 mg/kg, day 1), median treatment duration 45 weeks	Confirmed PSA50 and PSA <4 ng/mL	29.7%	21.6	Median, 20 weeks (range, 13–74)	Confirmed 50% PSA increase, and PSA >1 ng/mL
Beer et al. 2008 [6]	Randomized phase II	250, 1:1 randomized	DOC plus C (0.5 mg/kg, day 1) vs. DOC plus P	Confirmed PSA50 and PSA <4 ng/mL	N/A	18 overall (C 20 vs. P 16)	Median, 18 weeks (range, 4–70) overall (C 20 weeks vs. P 16 weeks)	Confirmed 50% PSA increase, and PSA >2 ng/mL
Olbert et al. 2009 [7]	Chart review	46	Variable DOC regimens (mostly weekly) ± EMP or mitoxantrone, 12-week treatment	Predefined 12 weeks of treatment	56%	NR	Not specified (≥ 3 months)	At least ≥3 months off DOC
Soga et al. 2009 [8]	Phase II	15	DOC 70 mg/m^2 q3 weeks plus EMP 560 mg p.o. o.d. days 1–5	At least 3 cycles of treatment and CR, PR or SD	NR	80 (9 pts after 3 cycles, 3 after 6 cycles)	NR	NR
Mountzios et al. 2011 [9]	Chart review	35	DOC 45 mg/m^2 biweekly, plus prednisone 5 mg b.i.d. (continued during DOC-free interval)	Confirmed PSA50 in the absence of progression	51.4%	51.4 (after a median of 6 infusions, mean time to first interval 2.9 ± 0.98 months)	Median, 4.5 months (range, 1–16)	Confirmed 25% PSA increase above nadir and PSA >10 ng/mL, or objective progression
Narita et al. 2012 [10]	Phase II	35	DOC 60 mg/m^2 day 1, carboplatin AUC5 day 1, EMP 560 mg p.o. daily (28-day cycles)	2 cycles	45.7%	40	NR	PSA above nadir
Li et al. 2013 [11]	Phase II (arm A), plus matching control arm B	Arm A: 42; arm B: 60	A: intermittent DOC 75 mg/m^2 q3 weeks plus bicalutamide; B: continued docetaxel 75 mg/m^2 q3 weeks without bicalutamide, 10–12 cycles	Confirmed PSA50, stable radiological findings, ≥3 cycles of DOC	66.7%	66.7	Median, 5.3 months (range, 2–20)	PSA increase ≥25%

Abbreviations: C, Calcitriol; DOC, docetaxel; EMP estramustine phosphate; NR, not reported; P, placebo; PSA, prostate-specific antigen; PSA50, >50% PSA response; q3, every 3.

Supplemental Table 2. Maintenance therapy

Reference	Study type	Patient population	*n*	Maintenance treatment details	Trigger for maintenance therapy	Results
Fizazi et al. 2009 [12]	Phase II, single-arm	Bone metastatic CPRC (after docetaxel at 70 mg/m^2 q3 weeks, plus EMP 10 mg/kg/d1–5 q3 weeks)	43	Docetaxel 20 mg/m^2 weekly $\times$ 6 plus Samarium-153-EDTMP (37 MBq/kg)	Response or SD after 4 treatment cycles, 42 pts entered maintenance phase of study	Primary endpoint PSA PFS: 6.4 months (95% CI 6–7 months); clinical PFS 15 months (11–29); PSA RR 77%; pain RR 60%
Nabhan et al. 2011 [13]	Phase II, single-arm	CRPC, after maximized docetaxel or mitoxantrone induction chemotherapy (details of regimens not provided)	15 evaluable for toxicity, 13 for efficacy	GM-CSF 250 μg/m^2 s.c. o.d. $\times$ 14 days (28 day cycles)	(A) $\geq$8 cycles, no signs of progression, and no wish to continue chemotherapy, or (B) $<$8 cycles but PSA drop $\leq$10% on two consecutive measurements and no signs of radiological progression, or (C) no progression 12 weeks after last chemotherapy	PSA response 15.3%; SD 30.7%; median time to PSA progression 6 months (4–12); radiological SD 69.2%; median time to radiological progression 6 months (2–10); median time to any type of progression 6 months (2–12)
Gil-Bazo et al. 2013 [14]	Chart review	CRPC, median of 7 cycles (range, 3–12) of docetaxel (75 mg/m^2 q3 weeks)	20 without progression evaluated (of 38 overall), 10 treated with maintenance low-dose ketoconazole, 10 without maintenance low-dose ketoconazole	Ketoconazole 200 mg p.o. t.i.d.	Biochemical response or stabilization to docetaxel in the absence of radiologic or bone scan progression	Median TTP from start of chemotherapy 11.5 months (6.3 - 16.6) with low-dose ketoconazole, 9.2 months (8.5 - 9.9) without low-dose ketoconazole, $p = .47$
Fuereder et al. 2014 [15]	Phase II, two-arm, randomized	CRPC, after induction therapy with docetaxel (75 mg/m^2 q3 weeks; $n = 3$) and sunitinib (37.5 mg/day p.o., 2 weeks on - 1 week off; $n = 8$)	8	Sunitinib 50 mg/day p.o., 2 weeks on - 1 week off, or no maintenance treatment	50% PSA response with no objective progression	PSA and/or objective PFS 2.6 months (1.4–2.9) with sunitinib maintenance versus 2.1 months (1.8–3.5) without sunitinib maintenance

Abbreviations: CRPC, castration-resistant prostate cancer; 95% CI, 95% confidence interval; EMP, estramustine phosphate; GM-CSF, granulocyte-macrophage colony stimulating factor; PFS, progression-free survival; PSA, prostate-specific antigen; q3, every 3; RR, response rate; SD, stable disease; TTP, time to progression.

Supplemental Table 3. mTOR inhibitor CRPC studies

Reference	Type of study	*n*	Patients	Treatment	Primary endpoint	Other results	Side effects	Comments
Armstrong et al. 2013 [26]	Open-label, single-arm phase II	11	Heavily pretreated, chemorefractory CRPC with ≥ 5CTCs	Temsirolimus 25 mg weekly i.v.	Change in CTCs at 8 weeks: median decline 48%, 3 pts decline to <5 CTCs/7.5 mL of blood	1 pt (9%) PSA30, any PSA decline 36.4%; 1 of 8 evaluable pts PR, 4 SD; PFS [excluding PSA] 1.9 months (95% CI 0.9–3.1), OS 8.8 months (3.1–15.6)	Grade ≥3 side effects in at least 2 pts: fatigue, muscle weakness, hypokalemia, anemia, hypokalemia	Study stopped prematurely because of lack of efficacy/ feasibility
Kruczek et al. 2013 [27]	Open-label, single-arm phase II	21 (15 evaluable for efficacy)	Chemotherapy-naïve CRPC	Temsirolimus 25 mg weekly i.v. (until voluntary withdrawal, toxicity, objective progression, or investigator's discretion; 4 week cycles)	Clinical benefit (overall response and SD rate): 13% + 54% = 67%	Median time to radiological progression, 2 months (range, 2–10); any PSA decline 28.5%, PSA50 7%, median time to PSA progression 2 months (range, 1–10); median overall survival 13 months (range, 2–37)	Most common grade 3/4 toxicities: thrombocytopenia 33%, lymphopenia 24%, hyperglycemia 24%, fatigue 19%, pneumonia 14%, anemia 14%, hypophosphatemia 14%; 52% of pts with SAEs; no negative impact on QoL (BPI and MDASI scales); 8 pts required dose reductions (5 pts because of thrombocytopenia)	Sponsor halted study early (after accrual of 21 of planned 25 pts); median of 2 cycles of temsirolimus (1–11)
Nakabayashi et al. 2012 [28]	Open-label, single-arm phase II	36	CRPC (± 1 line of chemotherapy; previous chemotherapy for HSPC (2 pts), CRPC (3 pts) or both (1 pt); 85% with prior exposure to bicalutamide, of which 69% as second-line hormonal therapy)	Everolimus 10 mg p.o. o.d., and Bicalutamide 50 mg p.o. o.d.	Best overall response (PSA, measurable and bone metastatic disease) as per modified PCWG2 criteria: confirmed PSA responses 6%, SD 25%	TTP 8.7 weeks (range, 0–43.6); unconfirmed PSA30 17%, unconfirmed PSA50 11%	Most common grade 3 toxicities: 8% hyperglycemia; 6% fatigue; 6% anemia; 6% hyponatremia; 3% mucositis, rash, cough, creatine phosphokinase elevation and (peri) anal infection	Most common type of progression = PSA only progression (54%)
Templeton et al. 2013 [29]	Open-label, single-arm phase II	37	Chemotherapy-naïve CRPC	Everolimus 10 mg p.o. o.d.	PFS at week 12 (PSA, radiographic and/or clinical): 35%	PFS 2.8 months (95% CI 1.9–3.6); PSA50 5%, PSA30 16%; numerous translational analyses, including correlation of longer PFS with PTEN deletion ($p = .07$)	Grade 3 toxicities in more than 1 pt: 8% anemia, 8% lymphopenia, 5% pain, 5% infection; no grade 4 events	Median duration of treatment 16 weeks (range, 0.3–48); no bone scan progressions at week 12

Amato et al. 2012 [30]	Open-label, single-arm phase II	38	Progressive taxane-treated CRPC	Ridaforolimus 50 mg weekly i.v.	RECIST1.0: PR 0%, SD 47.4%	PFS 28 days; PSA SD 21.1%, no PSA50; median time on treatment 109.5 days (1–442)	"generally well tolerated"; 6 pts discontinued treatment because of treatment-related AEs	PSA-alone progressors allowed to continue treatment; 14 pts not assessable for primary endpoint
Meulenbeld et al. 2013 [31]	Open-label, safety lead-in trial	11 (plus 1 screen failure)	Chemotherapy-naïve CRPC, without antiandrogen use within the last 4 weeks	Ridaforolimus 30 mg p.o. day 1, then 5/7 days starting day 8, and Bicalutamide 50 mg p.o. o.d. starting day 2	Safety and tolerability: 36.4% at least one grade ≥3 treatment-emergent AE, 72% of planned dose of ridaforolimus	PK analysis: ridaforolimus levels similar before versus after bicalutamide comedication; PSA50 27%, PSA30 36%	See primary endpoint	Study terminated after safety lead-in because of 3 pts with DLTs
Armstrong et al. 2010 [32]	Phase I	32	Men with intermediate- to high-risk prostate cancer undergoing radical prostatectomy	Rapamycin 3 mg p.o. o.d. × 14 days ($n = 20$), or 6 mg p.o. o.d. × 14 days ($n = 2$) before prostatectomy; control ($n = 10$)	Inhibition of S6 phosphorylation in pretreatment biopsy vs. prostatectomy samples: median inhibition of 58% in 50% of evaluable pts ($n = 10$) receiving 3 mg of rapamycin	PSA decline 27% (3 mg cohort), not further specified; no relevant effects on tumor cell proliferation or apoptosis	3 mg cohort no grade ≥3 side effects; DLT in both pts of 6 mg cohort - thrombocytopenia, stomatitis	

Abbreviations: CRPC, castration-resistant prostate cancer; 95% CI, 95% confidence interval; CTC, circulating tumor cell; DLT, dose-limiting toxicity; HSPC, hormone-sensitive prostate cancer; OS, overall survival; PCWG2, Prostate Cancer Working Group 2; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; pt(s), patient(s); PSA, prostate specific antigen; PSA30, ≥30% PSA response; PSA50, ≥50% PSA response; PTEN, phosphatase and tensin homolog; QoL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; (S)AE, (serious) adverse event; SD, stable disease; TTP, time to tumor progression.

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