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# A phase II study evaluating the toxicity and efficacy of single-agent temsirolimus in chemotherapy-naïve castration-resistant prostate cancer

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**Background:** The mammalian target of rapamycin (mTOR) pathway is deregulated in castration-resistant prostate cancer (CRPC). We investigated the efficacy and toxicity of temsirolimus, an mTOR inhibitor, in chemotherapy-naïve CRPC.

**Methods:** In this phase II open label study, eligible patients received IV temsirolimus at 25 mg weekly until objective disease progression, unacceptable toxicity or investigator's discretion. Toxicity was assessed every 4 weeks and responses every 8 weeks. Primary end point was calculating the overall response (OR) rate as well as measuring stable disease (SD) to assess the overall clinical benefit calculated as OR + SD. Secondary end points included prostatic-specific antigen (PSA) changes and time to progression biochemically and radiographically. Correlative studies included prospective assessment of quality of life (QoL) using two previously validated scales.

**Results:** Although the sponsor halted the study early, 21 patients were enrolled of which, 15 were evaluable for efficacy and OR. Median age was 74 (range: 57–89), median PSA was 237.5 ng ml<sup>-1</sup> (range: 8.2–2360), visceral disease present in 11 patients (52%), and 17 patients (81%) patients had Gleason score (7–10). Two patients had a partial response (PR) and eight had SD. The OR was 13% (2/15) and the overall clinical benefit (OR + SD) was 67% (10/15). Median time to radiographic disease progression was 2 months (range 2–10 months). Biochemical response assessment was available for 14/15 patients. Any PSA decline was observed in four patients (28.5%; 4/14) with one patient (7%) having >50% PSA decline. Median time to progression by PSA was 2 months (range 1–10 months). With a median follow-up of 32 months, median overall survival (OS) was 13 months (range: 2–37) and three patients remain alive at the data cutoff (5/2013) for an OS of 14% at 4 years on an intent-to-treat analysis. Major non-haematologic toxicities included fatigue (19%) and pneumonia (14%). Main laboratory toxicities included hyperglycaemia (24%) and hypophosphatemia (14%). Also, 52% of enrolled patients had serious adverse events. Other toxicities were consistent with previously reported adverse events with temsirolimus. Despite these observed adverse events, temsirolimus did not adversely impact QoL.

**Conclusion:** Temsirolimus monotherapy has minimal activity in chemotherapy-naïve CRPC.

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With close to 30 000 deaths annually, prostate cancer remains the second most common cause of cancer-related deaths in US men (Siegel *et al*, 2013). Further, this disease carries substantial morbidity and mortality in European countries. (Shibata and Whittemore, 2001; Neppel-Huber *et al*, 2012) Although therapeutic choices for castration-resistant prostate cancer (CRPC) have expanded recently beyond docetaxel-based chemotherapy, median survival remains suboptimal at less than 2 years. (de Bono *et al*, 2010; Kantoff *et al*, 2010; de Bono *et al*, 2011; Scher *et al*, 2012).

Multiple mechanisms for the emergence of CRPC have been proposed and continue to be investigated. (Debes and Tindall, 2004) These have been generally divided into pathways dependent on the androgen receptor (AR) and others that are activated independent of the AR (Chen *et al*, 2004). Understanding the molecular aspects of CRPC evolution has allowed for the development of targeted agents specifically designed to inhibit pathways implicated in the proliferation and growth of malignant cells (Nabhan *et al*, 2011). The phosphatase and tensin homologue (PTEN) tumour suppressor gene is commonly mutated in CRPC eliminating the inhibitory effect on the phosphatidylinositol 3-kinase (PI3K) pathway causing overproduction of AKT and subsequent cell proliferation and survival (Li *et al*, 1997; Debes and Tindall, 2004). Whether PTEN mutations contribute to the evolution or to the development of CRPC remains debated (Pourmand *et al*, 2007). Notably, This PI3K/AKT/mammalian target of rapamycin (mTOR) pathway has been linked to both tumorigenesis and resistance to therapy in prostate cancer and in other solid tumours as it is often deregulated during disease progression (Burgio *et al*, 2012).

Temsirrolimus is an mTOR inhibitor that is currently approved for treatment of patients with metastatic renal cell carcinoma including the subset with adverse prognostic features (Gore, 2007). Given the importance of this mTOR pathway in CRPC evolution and the witnessed activity of temsirolimus in renal cancer, we sought to investigate whether temsirolimus has activity in patients with CRPC that are chemotherapy-naïve. Herein, we report the final results of this phase II, open label, single-institution study.

## PATIENTS AND METHODS

**Patients.** Eligible patients were  $\geq 18$  years of age, with a diagnosis of CRPC per standard definition. (Scher *et al*, 2008) Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 2$  with measurable disease biochemically (using serum prostatic-specific antigen (PSA) measurements, with PSA of at least  $5 \text{ ng ml}^{-1}$  at baseline) and/or radiographically (using bone scans and/or computed tomography of measurable disease areas). Patients were required to have adequate bone marrow function (absolute neutrophil count  $\geq 1000 \mu\text{l}^{-1}$ , haemoglobin  $\geq 9.0 \text{ g dl}^{-1}$ , platelets  $\geq 100\,000 \mu\text{l}^{-1}$ ), adequate liver function tests (ALT/AST  $< 3 \times \text{ULN}$ , total bilirubin of  $1.5 \text{ mg dl}^{-1}$  or less), and creatinine of  $\leq 2.0 \text{ mg dl}^{-1}$ . Exclusion criteria included prior systemic chemotherapy for CRPC, prior exposure to temsirolimus, known HIV positivity, known brain metastases, and the use of any other experimental drug therapy within 28 days of study entry. Patients were allowed to receive intravenous or oral bisphosphonates for their bone metastases and were mandated to continue androgen suppression therapy while on study. Steroids were allowed concomitantly only if they were taken for another chronic medical condition. All subjects signed the written informed consent that was reviewed by the local institutional board as dictated by the declaration of Helsinki for human subject protection.

**Study design.** Patients received temsirolimus 25 mg per week given as a 30–60 min intravenous infusion on days 1, 8, 15, and 22

repeated every 28 days in this open label study. Four weeks of therapy constituted one cycle of treatment. Treatment continued until voluntary withdrawal, toxicity, objective disease progression, or the investigator's discretion. The trial was registered at www.clinicaltrials.gov (NCT00919035).

**Study objectives and end points.** The primary end point was calculating the sum of the complete response (CR), partial response (PR), and stable disease (SD) on radiographic imaging. All responses were confirmed using the PSWG-2 criteria. Complete response was defined as the disappearance of all measurable lesions including bone lesions detected on bone scans, no evidence of new lesions, and no disease-related symptoms. Partial response was defined as more than 30% decreases in the sum of the longest diameter of measurable lesions compared with baseline. Stable disease was defined as no significant decrease in lesions to constitute PR or CR and no sufficient increase to meet criteria for progressive disease (PD). Progressive disease was defined as more than 20% increase in the sum of the longest diameter of measurable lesions compared with baseline, and/or evidence of new lesions on imaging studies, the appearance of two or more new bony lesions on a bone scan, or newly developed cord compression or pathologic fracture. Percentage of patients achieving SD was calculated and defined as these who are achieving a clinical benefit without actual radiographic response. Secondary end points were toxicity, time to disease progression, PSA response, overall survival (OS), and the impact of temsirolimus on quality of life (QoL). Prostatic-specific antigen responses were measured as per Scher *et al* (Scher *et al*, 2008).

**Assessments.** Baseline evaluation included a complete history and physical exam including vital signs and performance status, complete blood count, comprehensive metabolic panel, fasting lipid panel, serum testosterone measurement, 12-lead electrocardiogram, CT-scans of measurable disease areas, bone scan, and brain imaging where indicated clinically. Responses were assessed every 8 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST) (Tsuchida and Therasse, 2001; Therasse *et al*, 2006). PSA was measured every 8 weeks. Quality of life measures were assessed prospectively using two previously validated scales; the Brief Pain Inventory (BPI) and the M.D. Anderson Symptom Inventory (MDASI) (Cleeland and Ryan, 1994; Cleeland *et al*, 2000).

**Safety and dosing.** Toxicity was documented every 4 weeks using the latest version of the Common Toxicity Criteria for Adverse Events (CTCAE) at the time of initiating the study. Temsirolimus dose was held for absolute neutrophil count  $< 1000 \mu\text{l}^{-1}$ , platelet count  $< 75\,000 \mu\text{l}^{-1}$ , or grade 3 adverse event. Once toxicities resolve to grade 2 or less, the drug was resumed at 5 mg per week lower dose (i.e., 25 mg weekly became 20 mg weekly, and if the patient was on 20 mg weekly dose became 15 mg weekly). Patients who required a dose reduction to less than 15 mg weekly were taken off study.

**Quality of life.** Quality of life and pain assessments were performed at baseline and every 8 weeks thereafter. A component score for the MDASI symptom severity scale was obtained using the average score for the first 13 items. The mean of the interference items (questions 14–19) was used to represent overall symptom distress (Fleming *et al*, 2012). Pain interference was scored as the mean of the seven interference items of the BPI (Gore, 2007).

**Statistical analysis.** The study aimed at enrolling 25 patients. Based on Simon two-stage phase II design, seven patients would be enrolled initially. If  $< 1$  response or SD was observed, the study would be stopped and the drug would be deemed ineffective. If  $> 2$  responses or SD were seen, the study would continue to accrue additional 18 patients for the total of 25 patients. If six or fewer

responses or SD were observed out of these 25 patients, the drug would be deemed ineffective. If seven or more responses or SD, the drug would be considered effective and worthy of further investigation. This sample would provide an 80% power to detect a clinical benefit defined as the sum of CR, PR, and SD between 15 and 40% (Type I error is controlled at 0.05 level). In 2012, after 21 patients were enrolled, the funding source (Pfizer) withdrew support to this study; accordingly, the trial was closed and halted accrual.

**RESULTS**

**Patients and disease characteristics.** Between 2009 and 2012, 21 patients were enrolled and 15 were evaluable for response. The remaining six patients completed less than two cycles of temsirolimus and hence were included only in the toxicity analysis. Baseline demographics are shown in Table 1. Median PSA was 237.5 ng ml<sup>-1</sup> (range 8.2–2360.6). Sites of metastatic disease included bone only (*n* = 6), bone and visceral disease (*n* = 11), bone and lymph node involvement (*n* = 3), and lymph node involvement only (*n* = 1). Median time on androgen deprivation therapy before study enrolment was 60 months (range 17–240 months).

**Efficacy results.** Fifteen patients were evaluable for radiographic response. Although no patient had a CR, two patients had a PR, eight demonstrated SD, and the remaining five patients had PD. Partial response patients were confirmed as per the PCWG2 criteria. The overall response rate (OR) was 13% (2/15) and the overall clinical benefit (OR + SD) was 67% (10/15). Median time to radiographic disease progression was 2 months (range 2–10 months).

Biochemical response assessment was available for 14/15 patients (one patient had no PSA at study exit per his choice).

Any PSA decline was observed in four patients (28.5%; 4/14) with one patient (7%) having > 50% PSA decline (Figure 1). Prostatic-specific antigen declines were confirmed as per the PCWG2 criteria. No changes to PSA doubling times were observed while patients were on study. Median time to progression by PSA was 2 months (range 1–10 months). With a median follow-up of 32 months, median OS was 13 months (range: 2–37) and three patients remain alive at the data cutoff (5/2013) for an OS of 14% at 4 years on an intent-to-treat analysis.

Subsequent therapies were captured for enrolled patients. Eight patients (38%) received systemic chemotherapy, four (19%) were treated with sipuleucel-T, five patients (24%) declined additional therapy, and one patient (5%) received palliative radiotherapy.

**Toxicity and adverse events.** A median of two cycles of temsirolimus was (Tables 2 and 3) administered (range: 1–11 cycles). Two patients (10%) completed 10 cycles of treatment, before demonstrating disease progression. In total, eight patients (38%) required dose reductions, five of which were related to thrombocytopenia. The three other dose reductions were related to fatigue and hypertriglyceridemia. Three of these eight patients required subsequent dose reductions due to thrombocytopenia.

All 21 patients were evaluable for toxicity. The most common Grade 3 or 4 toxicities were fatigue in 19%, pain, and pneumonias in 14% each. Grade 3 or 4 laboratory abnormalities were also noted. Thrombocytopenia (33%); hyperglycaemia (24%); and lymphopenia (24%); were the most common. Serious adverse events (SAEs) occurred in 11 patients (52%). Serious adverse events included: urinary tract infection, dehydration, weakness, transient ischaemic attack, pneumonia, pain, renal failure, anaemia, urinary retention, shortness of breath, deep vein thrombosis, acute arterial ischaemia, fever, and intracranial bleed. Of the SAEs reported, anaemia was considered related to study drug, whereas the remaining SAEs were not or possible related. There were three deaths during the study period but none of these were linked to the study drug. One patient died from surgical complications of a gangrenous foot (related to long standing vascular disease and diabetes), another from intracranial bleed, and a third from disease progression.

**Quality of life data analysis.** Completed MDASI and BPI questionnaires were available for 14 patients after the initial baseline assessment. Comparison of the baseline scores to the scores at the final study visit showed no significant difference and no adverse impact of the drug on QoL. Three separate domains were evaluated, including symptom severity, symptom interference with daily life, and pain scores. Symptom severity was calculated by averaging responses to items 1–13 on the MDASI. Patients rated

Table 1. Baseline characteristics (*n* = 21)

Median age, years (range)	74 (57–89)
Time since diagnosis, months (range)	120 (17–331)
PSA (ng ml <sup>-1</sup> ), median (range)	238 (8.0–2.361)
Time on ADT <sup>a</sup> , months (range)	60 (17–240)
Alkaline phosphatase (U l <sup>-1</sup> ), median (range)	104 (57–869)
Analgesic use, n (%)	7 (33)
<b>Site of metastases, n (%)</b>	
Bone	6 (29)
Bone and visceral	11 (52)
Bone and lymph node	3 (14)
Lymph node	1 (5)
<b>ECOG performance status, n (%)</b>	
0	10 (48)
1	10 (48)
2	1 (5)
<b>Gleason score, n (%)</b>	
≥7	17 (81)
<7	3 (14)
Unknown	1 (5)
Abbreviations: ADT = androgen deprivation therapy; ECOG = eastern Cooperative Oncology group; PSA = prostatic-specific antigen.	
<sup>a</sup> Before starting the study.	



Figure 1. Waterfall Plot for PSA changes in the 14 patients evaluable biochemically.

Table 2. Treatment-related toxicity according to CTCAE v3.0 (n = 21)

Adverse event	Grade 1 or 2		Grade 3 or 4	
	No	Frequency (%)	No	Frequency (%)
<b>Nonhematologic</b>				
Pain	12	57	3	14
Anorexia	11	52	1	5
Fatigue	11	52	4	19
Constipation	9	43	0	0
Rash	8	38	0	0
Depression	6	29	0	0
Oedema	6	29	0	0
Mucositis	6	29	0	0
Weight loss	6	29	0	0
Neuropathy	5	24	1	5
Nausea	3	14	1	5
Dehydration	2	10	1	5
Pneumonia	1	5	3	14
Urinary tract infection	0	0	1	5
TIA	0	0	1	5
DVT	0	0	1	5
Stroke	0	0	1	5
<b>Laboratory abnormalities</b>				
Elevated triglycerides	11	52	1	5
Hyperglycaemia	11	52	5	24
Hypoalbuminemia	10	48	0	0
Hypocalcemia	8	38	1	5
High cholesterol	8	38	1	5
AST elevation	6	29	1	5
Elevated alk phos	5	24	1	5
Hypokalemia	5	24	0	0
Elevated creatinine	5	24	1	5
Hyponatremia	4	19	1	5
ALT elevation	2	10	0	0
Hypophosphatemia	2	10	3	14
<b>Haematologic</b>				
Leucopenia	16	76	0	0
Anaemia	13	62	3	14
Thrombocytopenia	9	43	7	33
Lymphopenia	8	38	5	24

Abbreviations: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DVT = deep vein thrombosis; TIA = transient ischaemic attack.

their symptoms on a scale of 0–10 with an average symptom severity score of 1.58 at baseline and 1.96 at final visit. Symptom interference score was evaluated using items 14–19 of the MDASI. Patients reported an average symptom interference score of 2.01 at baseline and 1.79 at the final visit. Similar results were obtained using the BPI scale. Within the limitation of these small numbers, none of these differences appeared statistically significant.

**DISCUSSION**

In this phase II study, we show that temsirolimus has minimal activity in chemotherapy-naïve CRPC. Biochemical responses were modest, but two patients had objective response radiographically. To our knowledge, this is the first report of activity of temsirolimus in this particular patient population.

In addition to its known indication in renal cell cancer, previous studies have demonstrated minimal single-agent activity of

Table 3. Summary of AEs

Patients	n (%)
Any AE	21 (100)
Any grade ≥3 AE	19 (90)
<b>Any grade ≥3 AE in ≥2 patients</b>	
Thrombocytopenia	7 (33)
Hyperglycaemia	5 (24)
Lymphopenia	5 (24)
Fatigue	4 (19)
Pain, pneumonia, Hypophosphatemia, anaemia	3 each (14)
SAE	11 (52)
On-study deaths	3 (14) <sup>a</sup>

Abbreviations: AE = adverse event; SAE = serious adverse event.  
<sup>a</sup>All not related to study drug (one from disease progression, one from surgical complications from gangrene related to diabetes and vascular insufficiency present before the study initiation, and one from intracerebral haemorrhage).

temsirolimus in cervical, breast, and epithelial ovarian cancer/primary peritoneal cancer (Behbakht *et al*, 2011; Fleming *et al*, 2012; Tinker *et al*, 2013). In these studies, however, responses were modest with some patients achieving disease stability radiographically. Toxicities were minimal and consistent with known adverse events reported in pivotal renal cancer studies. (Bhojani *et al*, 2008) In combination with bevacizumab, temsirolimus showed higher response rates in patients with advanced melanoma and relapsed endometrial carcinoma but these were marginal and short-lived (Alvarez *et al*, 2013; Slingluff *et al*, 2013). Although these studies showed marginal benefit, these results coupled with the accumulated evidence of the PTEN deregulation in advanced prostate cancer suggested that further investigation of temsirolimus in this setting is justified (Pourmand *et al*, 2007; Schmitz *et al*, 2007; Shen and Abate-Shen, 2007; de Muga *et al*, 2010).

In our study, disease stabilisation occurred in the majority of patients but two patients demonstrated PR radiographically. Stability of metastatic disease clinically and radiographically could provide metastatic incurable patients with an appreciable and meaningful benefit. Although it remains uncertain whether clinical benefit defined as SD correlates with OS in prostate cancer, this concept has been suggested in other solid malignancies (Takahashi *et al*, 2000; He *et al*, 2010; Kim *et al*, 2010). Early studies in prostate cancer suggested that PR and SD patients treated with cytotoxic therapy might derive similar therapeutic benefit. (Slack *et al*, 1980, 1984) However, modern studies have yet to demonstrate similar findings. We propose that further understanding of the impact of SD on survival and other outcome measures warrant rigorous investigation.

Observed toxicities in our study were predictable. Myelosuppression was notable, as five patients required a dose reduction owing to thrombocytopenia and three of these required an additional dose reduction for the same reason. Thrombocytopenia has been reported in nearly all studies of temsirolimus and in most cases was mild and manageable. Additional laboratory toxicities of hyperglycaemia (24% grade 3/4) and hyperlipidemia (5% grade 3/4 and 38% grade 1/2) were also observed. Interestingly, it has been reported that patients with renal cell carcinoma who have elevation in cholesterol while receiving temsirolimus have superior survival compared with others with no changes in cholesterol values. (Lee *et al*, 2012) Additional grade 3/4 adverse events were observed; fatigue (19%), pneumonia (14%), and pain (14%). Further, 52% of patients encountered SAEs. However, these witnessed toxicities in our study did not affect QoL of treated patients. Incorporating QoL

measures with traditional biochemical and radiographic responses remains challenging and is not uniformly reported in prospective studies. Two previously validated and widely used scales were implemented in this study. The MDASI and BPI assessed symptom severity, interference in daily life, and the average pain score at each study visit. Neither of these scales was specific for patients with advanced prostate cancer. Nevertheless, the questionnaires in both scales addressed commonly encountered problems in patients with advanced malignancies. Our data show no significant adverse impact on QoL. Although there continues to be a debate as to what is the best measure to assess QoL, (Colloca and Colloca, 2011) establishing a consistent way of measuring QoL across trials will become increasingly important as more agents become available. Importantly, most QoL studies have generally focused on evaluating toxicities of early disease treatment (i.e., surgery, radiotherapy, ADT, and brachytherapy) (Hoskin *et al*, 2013; Komiya *et al*, 2013; Mc Caughan *et al*, 2013; van Tol-Geerdink *et al*, 2013) with fewer studies assessing the impact of cytotoxic chemotherapy (Caffo *et al*, 2011). Critically, as newer targeted agents become increasingly utilised in CRPC and as these agents have different toxicity profile than traditional chemotherapy, evaluating their impact on QoL will be essential moving forward.

Few studies explored the activity of mTOR inhibitors in CRPC. In a single-arm phase II study, 37 chemotherapy-naïve patients with CRPC were treated with everolimus continuously at 10 mg daily (Templeton *et al*, 2013). The primary end point of PFS at 12 weeks was met by 13 patients (35%) with 2 patients having >50% PSA decline. Armstrong *et al* (2013) conducted a phase II study with weekly temsirolimus in patients with chemotherapy-refractory CRPC who had more than five circulating tumour cells (CTCs) at baseline. Although the trial aimed at enrolling 20 patients, it was halted prematurely after 11 patients were treated due to lack of activity. However, this study's primary end point was the change in CTCs at 8 weeks and 73% of men had persistently unfavourable CTCs ( $\geq 5$ ) over time and only 1 patient had a  $\geq 30\%$  PSA decline. Median progression-free survival was 1.9 months and median OS was 8.8 months. These studies along with our report suggest that mTOR inhibitors have minimal activity in CRPC and a benefit might be observed earlier in the course of this disease before chemotherapy refractoriness. Further, studying these agents only in patients who manifest a PTEN mutation might prove beneficial.

The median OS of 13 months was less than ideal for a chemotherapy-naïve patient population. Whether this suggests that temsirolimus had an adverse impact on outcome cannot be determined. Other possibilities include the fact that only 38% of enrolled patients received chemotherapy after progression, whereas 24% of patients refused any additional therapy. This precluded patients from receiving some of the newer available agents that have become available. Since the inception of this trial, newer therapeutic interventions have become widely available for CRPC. In the asymptomatic setting, Kantoff *et al* (Kantoff *et al*, 2010) reported on the activity of sipuleucel-T, an autologous cellular immunotherapy, demonstrating that this agent improves OS when compared with control. The abundance of data showing continued AR activation even in the CRPC setting has led to developing agents targeting the AR pathway. Abiraterone, an androgen biosynthesis inhibitor, improved OS in CRPC patients who have failed docetaxel (de Bono *et al*, 2011) and also approved in the chemotherapy-naïve setting (Ryan *et al*, 2013). Enzalutamide, an AR inhibitor, was also shown to improve OS in CRPC patients who failed prior chemotherapy (Scher *et al*, 2012). The availability of these newer therapies in the same space where our study was conducted might have led the sponsor to halt the study prematurely, as difficulty in accruing patients was anticipated with more available commercial treatment choices. However, the cross talk between the AR and mTOR pathways that has been

established in several *in vitro* studies might lead to suggest combining agents targeting both pathways for ultimate inhibition of CRPC progression (Lin *et al*, 2004; Carver *et al*, 2011; Wang *et al*, 2011).

As current and future newer therapies will become available for patients with CRPC, exploring whether mTOR inhibitors have any future roles in CRPC is challenging. The collective evidence suggests that mTOR inhibitors' activity is limited to a small subset of patients. We propose that future studies with these agents are limited to combination programs with other targeted agents, preferably these targeting the AR pathway.

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