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A Phase 2 Study of GW786034 (Pazopanib) with or without Bicalutamide in Patients with Castration Resistant Prostate Cancer

Srikala S. Sridhar[1], **Anthony M. Joshua**[1], **Richard Gregg**[2], **Christopher M. Booth**[2], **Nevin Murray**[3], **Jovana Golubovic**[1], **Lisa Wang**[1], **Pamela Harris**[4], and **Kim N. Chi**[3]

[1]Princess Margaret Hospital, Phase II Consortium, Toronto, ON

[2]Department of Oncology, Queen's University, Kingston, ON

[3]BC Cancer Agency, Vancouver, BC

[4]Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD

Abstract

Introduction—Pazopanib is an oral vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor. In this randomized open label phase II study, pazopanib alone or in combination with bicalutamide was evaluated in chemotherapy-naive castration resistant prostate cancer (CRPC) patients.

Methods—Patients received either pazopanib 800 mg daily (Arm A) or pazopanib 800 mg plus bicalutamide 50 mg daily (Arm B). A two-stage study design was used and the primary endpoint was PSA response rate (defined as a confirmed ≥50% decline from baseline).

Results—Twenty-three patients (Arm A 10, Arm B 13) were accrued. The main grade 3+ toxicities were hypertension, fatigue, decreased lymphocytes and increased ALT. Due to significant toxicity, the protocol was amended after the first 11 patients and the pazopanib starting dose was reduced to 600 mg daily. In arm A, of 9 evaluable patients there was 1(11%) patient with a PSA response, 3 (33%) with stable PSA, and 5 (56%) with PSA progression; in arm B of 12 evaluable patients: there were 2 (17%) patients with PSA responses, 6 (50%) with stable PSA and 4 (33%) with PSA progression. Median PFS (95%CI) was similar in both arms at 7.3 months (2.5 mo-not reached). Long term SD was seen in 4 patients who remained on treatment for 18 (Arm A), 26 (Arm A), 35 (Arm B) and 52 (Arm B) months.

Corresponding Author: Kim N. Chi, BC Cancer Agency – Vancouver Centre, 600 West 10th Avenue, Vancouver, British Columbia, Canada, V5Z 4E6, kchi@bccancer.bc.ca, Phone: 604-877-6000, Fax: 604-877-0585.

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Conclusions—In this unselected patient population, pazopanib either alone or in combination with bicalutamide failed to show sufficient activity to warrant further evaluation. However, four patients did had long-term benefit suggesting that targeting VEGFR pathway may still be relevant in selected patients, emphasizing the need for improved predictive markers for patients with CRPC.

Introduction

Prostate cancer is the most commonly diagnosed and second leading cause of cancer related death among men in North America. In the US in 2013 approximately 238,590 patients will be diagnosed and 29,720 will die of this disease [1]. Although primary androgen deprivation therapy is effective in treating patients with recurrent or metastatic prostate cancer, development of castration resistant prostate cancer (CRPC) remains inevitable. Initial treatment of CRPC involves secondary hormonal manipulations with the addition of an oral non-steroidal anti-androgen such as bicalutamide. Although well tolerated, bicalutamide has a PSA response rate of only 20% and a limited duration of benefit, underscoring the need for new treatment approaches [2-4].

Angiogenesis, mediated by the vascular endothelial growth factor receptor pathway (VEGFR) may be a good target in prostate cancer because it has been implicated in both the development and progression of the disease [5, 6]. In three studies in prostate cancer tumor tissue, increased microvessel density, a surrogate marker for angiogenesis, has been shown to correlate with both disease progression and decreased survival [6-8]. Endothelial cells and prostate cancer cells from radical prostatectomy specimens express VEGFR, suggesting VEGFR signaling may promote both angiogenesis and direct tumor cell proliferation [5].

Studies have shown that median levels of plasma VEGF are significantly higher in patients with metastatic disease compared to those with localized prostate cancer [9] and that elevated plasma and urine levels of VEGF may be independent negative prognostic indicators [10, 11]. These findings suggest that inhibiting the VEGFR pathway might be an effective approach in prostate cancer.

Initial clinical trials of angiogenesis inhibitors in prostate cancer have shown limited activity and no improvement in overall survival [12]. More recent studies have focused on combining angiogenesis inhibitors with hormonal therapy or chemotherapy, based largely on preclinical studies showing that angiogenesis inhibitors may restore sensitivity to these agents [13-19].

Pazopanib is a novel small molecule tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and c-kit. Pazopanib is currently approved for the treatment of advanced renal cell carcinoma and for advanced soft-tissue sarcoma previously treated with prior therapy. The goal of this open label, randomized phase II study, was to evaluate the efficacy and tolerability of pazopanib alone and in combination with bicalutamide in patients with chemotherapy-naïve CRPC.

Patients and Methods

Eligible patients were ≥ 18, had an ECOG performance status of 0-2, a life expectancy > 3 mos, adequate organ function and confirmed prostate adenocarcinoma. At study entry all patients must have had radiological documentation of either measurable or non-measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.0). PSA had to be ≥ 5 ng/mL with evidence of progression (defined as ≥ 2 consecutive rises in PSA, at least 1 week apart) despite castrate testosterone levels (<50ng/mL). Patients must have been treated and maintained with medical (GnRH agonist) castration or undergone orchiectomy. Anti-androgens (flutamide, nilutamide or cyproterone acetate) were permitted but had to be stopped ≥ 4 weeks and ≥12 weeks for bicalutamide prior to enrollment. Treatment with steroids was permitted, but no change in dose within 4 weeks of study entry was allowed. Prior radiation was permitted provided ≥ 4 wks elapsed prior to study entry. Key exclusion criteria were prior chemotherapy, radioisotope therapy or investigational agents for CRPC; greater than 1+ proteinuria on two consecutive dipsticks at least 1 week apart; QTc prolongation (QTc interval ≥ 500 msecs) or other significant ECG abnormalities; poorly controlled hypertension (systolic blood pressure >150 mmHg, or diastolic blood pressure >90 mmHg); or any condition resulting in an inability to swallow and retain Pazopanib. Patients with known brain metastases or other significant medical illnesses were also excluded

Study Design and Treatment

This was a multi-institutional phase II study conducted by the Princess Margaret Hospital (PMH) Phase II Consortium, Cancer Therapy Evaluation Program, and the National Cancer Institute. The study was registered (ClinicalTrials.gov identifier NCT00486642) and ethics boards at all participating sites approved the study and patients signed a written informed consent form. Pazopanib is manufactured by GlaxoSmithKline (GSK) and was supplied by NCI CTEP. All patients in Arm A and B initially received pazopanib 800 mg daily. All patients in Arm B also received bicalutamide 50 mg daily continuously starting on day 8 of cycle 1. Pazopanib doses were adjusted for severe toxicity to either 600 mg or 400 mg. Due to adverse events in the first 11 patients, the starting dose of pazopanib was reduced to 600 mg daily for subsequent patients, with further dose reductions to 400 mg and 200 mg permitted for unacceptable toxicities.

Treatment continued on either arm until one of the following occurred: (1) disease progression: defined as either PSA progression (≥ 50% increase in PSA from nadir or baseline), objective disease progression by Response Evaluation Criteria in Solid Tumors criteria [20] or cancer-related symptomatic progression (new or worsening disease related symptoms requiring change in therapy, change in anti-neoplastic management, or disease related fall in ECOG performance status by ≥ 2 levels); (2) intercurrent illness that prevents further administration of treatment; (3) unacceptable adverse events; (4) patient decision to withdraw from the study or (5) investigator decision. Patients were allowed to remain on protocol therapy for a rising PSA/PSA progression provided there were no other indications of progression.

Baseline and follow-up studies

Baseline assessment included a history, physical, height, weight and assessment of ECOG Performance status. Baseline bloodwork included CBC with differential, serum chemistries, testosterone, PSA and urinalysis. Diagnostic tests performed at baseline included, EKG; chest x-ray or chest computed tomography (CT), and abdominal and pelvis CT scans and bone scan. Patients were evaluated clinically every 2 weeks, with PSA testing done every 4 weeks. Measurable disease was evaluated every 12 weeks.

Response Assessment

Patients receiving at least one cycle of therapy and having ≥2 PSA values at least 3 wks apart from baseline were evaluable for PSA response. PSA response was defined as a 50% decrease in PSA from baseline confirmed by a second PSA value ≥ 3 wks later. The PSA response duration began the date of the first 50% decline in PSA and ended when PSA increased by 25% over the nadir PSA with an increase of at least 5 ng/mL and confirmed by a second measurement [21]. Measurable response was evaluated using RECIST. All patients receiving treatment were assessable for toxicity.

Statistical Considerations

This was a multicenter, open label, non-comparative, randomized phase II study. The primary endpoint was PSA-response which has been correlated with improved survival outcomes for patients with rising PSA post castration therapy [22]. At the time this study was conducted PCWG2 criteria were not yet available [23], If a patient continued to have stable disease after 6 months of treatment, they were classified as a ‘responder’ for the statistical purpose of deciding whether or not to continue on to stage II. Pazopanib as a single agent (Arm A) was assumed to be inactive if the PSA-response/prolonged stable disease rate (PSA PR/SD) was at most 5% and active if it was at least 20% ($P_0 = 0.05$, $P_1 = 0.20$, $\alpha = 0.10$ and $\beta = 0.10$). For stage 1, the plan was to accrue 12 evaluable patients and if at least 1 patient had a PSA response or prolonged stable disease for ≥6 months (pSD), an additional 25 evaluable patients were to be accrued. In stage 2, If ≥4/37 patients had a PSA response/ pSD, treatment would be considered active. Pazopanib in combination with bicalutamide (Arm B) was assumed to be inactive if the PSA response/pSD was at most 20% and active if it was at least 40% ($P_0 = 0.20$, $P_1 = 0.40$, $\alpha = 0.09$ and $\beta = 0.09$). For stage 1, the plan was to accrue 17 evaluable patients. If at least 4 patients had a PSA response/pSD an additional 20 patients would be accrued. If >11/37 in stage 2 had a PSA response/pSD the treatment would be considered active. The secondary endpoint was progression free survival (PFS) defined as time from treatment initiation to disease progression or death from any cause. Since patients came off study when they had disease progression, excessive toxicity or withdrew from the study, no information regarding overall survival was collected.

Results

Patient Population and Treatments Administered

Between September 2007 and March 2011, 23 patients were accrued. There were 10 patients in Arm A and 13 patients in Arm B. Despite being a multi-institutional study, accrual to the

study was poor. Main reasons for poor accrual included competing trials with the newer hormonal agents (abiraterone and enzalutamide) which opened after the current trial; concerns over toxicity and lack of experience with pazopanib at the time; patients progressing too rapidly on hormonal therapy and requiring immediate chemotherapy; and delays related to the amendment for the dose reduction. Patient baseline characteristics are listed in Table 1.

Response

PSA Best Response—In arm A, of 9 evaluable patients there was 1 (11%) PSA response, 3 (33%) patients with stable PSA, and 5 (56%) with PSA progression. In Arm B, of 12 evaluable patients there were 2 (17%) PSA responses, 6 (50%) with stable PSA and 4 (33%) with PSA progression. Given the poor accrual to the study, following a teleconference amongst investigators, a decision was taken to halt accrual permanently. As a result of this decision, no adjustment to the statistical plan to account for lower accrual was required.

Measureable Disease Response—In Arm A, of 5 evaluable patients, there were 0 (0%) partial responses (PR), 2 (40%) stable disease (SD), and 3 (60%) with progressive disease (PD) as best response. In Arm B, of 9 evaluable patients, there was 1 (11%) PR and this patient also had had a PSA response; 8 (89%) SD, 0 with PD. Considering both arms together, overall RECIST response for 14 evaluable patients, the overall PR was 7%, SD in 71% and PD in 21% as best response. There was no clear evidence of discordance between bone scan responses and PSA increases, as has been seen previously with sunitinib in CRPC, although our study was relatively small [24].

PFS—There were 14 events (PD/death) in the 23 patients. Of these, 3 patients had PSA progression only, 1 had RECIST progression only, 2 had symptomatic progression alone while 5 had both PSA and RECIST progression and 3 had both PSA and symptomatic progression. Other patients were censored at last follow up. Median PFS (95%CI) was similar in both two arms (p=0.18) and estimated to be 7.3 months (2.5-not reached) (Fig. 1). There were four long term responders, 2 in each arm. The longest responder was on Arm B, had prior bicalutamide and stayed on study treatment for 52 months; at baseline he had a PSA of 66, Gleason 8 disease, with lymph node only disease and had both a PSA response and PR in measureable disease. Another patient also on Arm B, did not have prior bicalutamide and was on study for 35 months; at baseline he had a PSA of 40, Gleason score 7, with soft tissue, and bone metastases. A third patient on Arm A, had prior bicalutamide, and was on treatment for 26 months; baseline PSA was 64, Gleason 6, with bony metastases only; and the fourth patient also on Arm A, did not have prior bicalutamide and was on study for 18 months; baseline PSA 11, Gleason score 9, with adrenal, lymph node and bony metastases.

Adverse Events (AE)—The most common treatment emergent adverse events were fatigue, anorexia, hypertension and diarrhea. The most common grade 3 or higher adverse events were hypertension, fatigue, and decreased lymphocytes (Table 2). Of the first 11 patients who started at a dose of 800 mg daily, 6 patients required dose reductions to 600 mg

daily. The protocol starting dose was therefore amended to 600 mg daily. Of the 9 patients who started at 600 mg daily, 4 patients still needed further dose reductions to 400 mg daily and 1 patient went to 200 mg daily. Fatigue was the main dose-limiting toxicity All patients are now off study. Twelve patients came off-treatment due to PD, 9 due to toxicity, and 2 patients withdrew consent. The impact of pazopanib dose reductions on response is difficult to ascertain, but it is notable that all of the patients who experienced a prolonged PFS were on a reduced dose of pazopanib.

Discussion

Over the last three years several novel therapies have become available for the treatment of CRPC. These agents, including abiraterone acetate, enzalutamide, cabazitaxel and most recently radium-223, have all demonstrated improvements in overall survival in Phase III clinical trials [25-28]. However, none of these agents are curative, highlighting the need for ongoing research in the field.

Targeting the angiogenesis pathway has proven to be a well-tolerated and an effective approach in some cancers such as metastatic renal cell cancer [29]. In this open label Phase II study, chemotherapy naïve CRPC patients were randomized to receive pazopanib alone or with bicalutamide. Unlike the experience in mRCC, toxicities including fatigue, hypertension and diarrhea were significant enough to require a dose reduction in 40% of patients. Increased toxicities of the angiogenesis in inhibitors in prostate cancer has been previously reported, and it has been hypothesized that this may be due to the advanced age of this patient population (approximately ten years older than mRCC patients in the pivotal trials), comorbidities especially prior cardiovascular events, altered metabolism of the drug, effect of castration, or increased presence of bone-predominant disease [16, 30].

From an efficacy standpoint, given the small number of patients evaluated, it is difficult to draw firm conclusions, but it would appear that the results of this study are similar to previous larger studies of angiogenesis inhibitors in CRPC. For example, sunitinib, another VEGFR TKI, showed few PSA responses, despite biomarker studies confirming its on-target effects. Interestingly in the sunitinib study, radiographic responses were seen, but were discordant with PSA change, suggesting that PSA response may not necessarily be the ideal endpoint for clinical trials evaluating VEGF/VEGR targeted therapy [24]. Discordance was also seen in two negative studies with the VEGF/ERK kinase inhibitor sorafenib, where it was suggested that sorafenib may even directly impact on PSA production or secretion, independent of antitumor activity [31, 32]. Similar challenges have also been faced when evaluating immunotherapy in CRPC. One example is sipuleucel-T, an autologous dendritic vaccine targeting prostatic acid phosphatase which was tested in men with asymptomatic or minimally symptomatic mCRPC. Sipuleucel T treated patients showed a significantly improved OS compared to placebo, but as in earlier trials, there was no difference in time to radiographic or PSA progression and few declines in PSA, again underscoring the challenges of defining endpoints for trials of new agents in CRPC [33]. More recent studies of angiogenesis inhibitors in combination with chemotherapy have used PFS or OS as endpoints. A Phase III trial of docetaxel with aflibercept (a decoy VEGF) compared to docetaxel alone did not improve survival, and though bevacizumab (a recombinant anti-

VEGF monoclonal antibody) when added to docetaxel did improve PFS, again there was no significant improvement in OS compared to docetaxel alone [16, 30]. Developing and validating clinically relevant endpoints for trials of new agents in CRPC has become increasingly important, because many of the newer agents like the angiogenesis inhibitors and immunotherapy may not have as predictable an effect on standard parameters of PSA response, radiographic response, PFS or OS as the older hormonal or cytotoxic agents used in this disease.

As with our study, all of the other studies of angiogenesis inhibitors were conducted in unselected patient populations, but also consistent across these studies was that fact that there were small populations of patients who did respond, and sometimes for prolonged periods of time. In our study, there were 4 patients of which two had prior bicalutamide and showed long term stable disease on treatment. One of these patients, on Arm B, who had prior bicalutamide, and lymph node only disease had both a PSA response and a measureable disease response, and stayed on treatment for 52 months. Developing predictive biomarkers may help to determine which patients are more likely to respond to these agents. To date however, studies evaluating the utility of angiogenic factors such as VEGF, VEGFR and others, across different tumor types treated with different angiogenesis inhibitors, has not yet resulted in a validated predictive biomarker platform, though research in this area is actively ongoing [34] .

In CRPC, the limited responses and resistance to angiogenesis inhibitors has led to the search for factors that may specifically mediate this resistance and allow tumor progression. There is growing interest in the MET signaling pathway, which appears to be upregulated in response to both anti-angiogenic therapy and hypoxia [35]. Preclinical studies have suggested that targeting both VEGF and MET concurrently with the TKI, cabozantanib, is a rational therapeutic approach [36]. In mouse xenografts, cabozantanib inhibited tumor growth in bone and soft tissue, irrespective of whether the mice were castrate or not [37]. In Phase II testing, cabozantinib has shown impressive clinical responses, including reduction of soft tissue lesions, improvement in PFS, resolution of bone scans and reductions in markers of bone turnover, decreased pain and narcotic use and has now moved into Phase III testing [38, 39].

Clearly, further research is required to identify predictors of response or resistance to these and other new agents in CRPC. Large scale multi-center efforts to molecularly profile tissues from biopsies on patients with CRPC progressing on therapy will potentially lead to such advances and a precision medicine approach (http://www.aacr.org/home/public--media/stand-up-to-cancer/su2c-dream-teams/). In this study, the anti-tumor activity of pazopanib either alone or with bicalutamide in an unselected population of chemo-naïve CRPC patients with progressive disease, does not warrant further study. However, several patients did have long-term benefit, suggesting that targeting the VEGFR pathway remains relevant in selected patients and emphasizes the need for developing of improved predictive markers for patients with CRPC.

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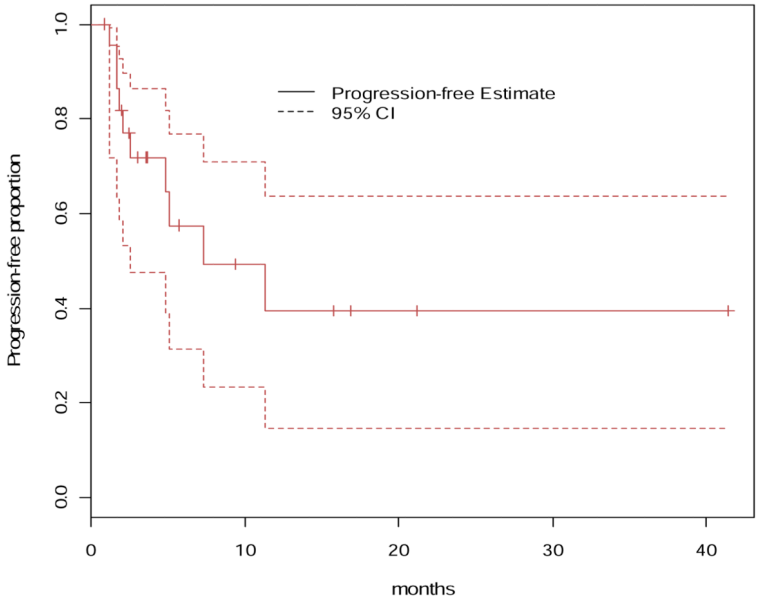

Fig. 1. Progression Free Survival Curves. Median PFS (95% CI) 7.3 (2.5-not reached months)

Table 1

Patient Characteristics

	Number of Patients	Median (Range)
Total Patients Entered	23	
Median Age (Range) (yrs)		71 (51-85)
Performance Status		
ECOG 0	16	
ECOG 1	17	
Baseline Sites of Disease		
Bone Only	5	
Node Only	2	
Visceral Disease Only	2	
Multiple Sites(Bone, Node, Visceral)	14	
PSA (ug/L)		136 (11-1200)
Hemoglobin (g/L)		129 (76-151)
Alkaline Phosphatase (U/L)		145 (54-595)
Lactate Dehydrogenase (U/L)		207 (141-462)
Prior Hormonal Therapy		
Medical/Surgical Castration only	2	
Combined Androgen Blockade with prior bicalutamide	21	
Radiation Therapy	18	

Table 2

Treatment Emergent Adverse Events of patients treated with pazopanib with or without bicalutamide

Adverse Event	All Grades Number of Patients	Grade ≥3 Number of Patients
Fatigue	16	5
Anorexia	14	1
Hypertension	13	6
Diarrhea	13	-
Increased AST	11	1
Proteinuria	10	-
Increased ALT	9	1
Decreased Lymphocytes	8	2