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# A phase II trial of the Src-kinase inhibitor AZD0530 in patients with advanced castration-resistant prostate cancer: a California Cancer Consortium study

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**Prostate cancer cells undergo neuroendocrine differentiation during androgen deprivation and secrete neuropeptides, hence activating androgen receptor-regulated genes. Src-family protein kinases are involved in neuropeptide-induced prostate cancer growth and migration. A phase II trial of AZD0530, an oral Src-family kinase inhibitor, in patients with advanced castration resistant prostate cancer was conducted. The primary endpoint was prostate cancer-specific antigen (PSA) response rate, defined as a 30% or greater decrease. A two-stage Simon design was used. Eligibility criteria included documentation of castration resistance (including antiandrogen withdrawal), adequate end-organ function, and performance status, and not more than one prior taxane-based chemotherapy regimen. AZD0530 was given at 175 mg orally once daily continuously. Rapid accrual led to 28 patients registering in the first stage. Median age was 67 years. Sixteen patients had performance status (PS) 0, eight patients had PS 1, and four patients had PS 2. Nine patients (32%) had prior docetaxel-based chemotherapy. Five patients had transient PSA reductions not meeting PSA response criteria. Median progression-free survival time was 8 weeks. Treatment was generally well tolerated. AZD0530, a potent oral Src kinase inhibitor, is feasible and tolerable in this pretreated patient population but possessed little clinical efficacy as monotherapy. Strong preclinical evidence warrants further investigation of AZD0530 in earlier-stage prostate cancer or as combination therapy.** *Anti-Cancer Drugs* **20:179–184 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Prostate cancer is the most common cancer in American men and the second leading cause of cancer deaths [1]. In most treatment-naive patients with metastatic prostate cancer, androgen deprivation (castration) therapy can induce substantial tumor reduction and disease control. Unfortunately, prostate cancer cells subsequently lose androgen dependency, leading to a metastatic and androgen-independent state, often termed as castration-resistant prostate cancer [2]. The vast majority of deaths from prostate cancer is due to castration-resistant disease.

During the transition to castration resistance, a subpopulation of neuroendocrine cells appears to expand [3,4]. Nearly all prostate cancers contain neuroendocrine cells that are identified by neurosecretory granules and the expression of neuron-specific markers including chromogranin A, neuro-specific enolase, and mitogenic hormones such as parathyroid hormone-related peptide, bombesin/gastrin-releasing peptide, serotonin, calcitonin, and neurotensin, among others [5–10]. However, during castration therapy, more prostate cancer cells acquire neuroendocrine features and begin expressing neuropeptides. Through nonreceptor tyrosine kinases, these neuropeptides activate androgen receptor-regulated genes in the absence of androgens to support growth, migration, and in-vivo metastasis [11]. Furthermore, cytokines such as IL-6 and IL-8 have increased expression at the time of castration and induce nonreceptor tyrosine kinase-mediated androgen-independent prostate cancer [12].

Members of the Src family of protein kinases have been identified as involved in neuropeptide-induced cell growth and migration [13]. Src, the first oncogene to be identified, mediates the signaling of a number of

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neuropeptide receptors and is involved in formation of focal adhesions and enhanced cellular migration. Src regulates signaling pathways involving survival, angiogenesis, steroid receptor activation, and growth factor receptors [14]. Increased Src activity appears to correlate with disease progression. In addition, it has been reported that Src is not only activated in androgen-sensitive LNCaP cells upon androgen withdrawal, but is constitutively activated in several castration-resistant cell lines [15]. Novel agents that modulate the Src-kinase pathway offer the potential for therapeutic advances in castration-resistant prostate cancer.

AZD0530 is a novel, orally bioavailable aniline–quinazoline that has been shown to modulate cellular pathways involving the Src family of kinases. AZD0530 is highly selective for nonreceptor tyrosine kinases with $IC_{50}$ values in the nanomolar (nmol/l) range for several targets, including c-Src (2.7 nmol/l), c-Yes (4 nmol/l), Lck ( < 4 nmol/l), and Bcr-Abl (30 nmol/l). In nonclinical models, AZD0530 has demonstrated potent effects on cell motility, invasion, and metastasis. It is a dual-specific inhibitor that acts through ATP competitive and reversible inhibition of target enzymes. Preclinical work with AZD0530 in prostate cancer cell lines (LNCaP, PC3, DU145, and CWR22R) showed that all lines expressed phospho-Src and treatment with AZD0530 (5 μmol/l) inhibited Src activation [16]. In an in-vivo murine xenograft model of neuroendocrine prostate cancer, AZD0530 was found to inhibit tumor Src phosphorylation as well as tumor growth in a dose-dependent manner. In addition, prostate cancer cell migration was decreased by AZD0530 through phospho-focal adhesion kinase inhibition.

A phase I clinical trial showed the feasibility and tolerability of AZD0530 treatment in patients with advanced solid malignancies and provided the first demonstration of pharmacological Src inhibition in tumor tissue of patients with cancer [17]. In light of these results, and the preclinical evidence of activity in prostate cancer, we conducted a phase II trial of AZD0530 in patients with advanced, castration-resistant prostate cancer.

## Patients and methods

### Eligibility criteria

To be eligible, all patients must have had a histologic diagnosis of adenocarcinoma of the prostate that was unresponsive or refractory to hormone therapy (despite androgen deprivation and anti-androgen withdrawal when applicable) as defined by at least one of the following criteria: (i) progression of unidimensionally measurable disease assessed within 28 days before initial administration of drug; (ii) progression of evaluable but not measurable disease assessed within 28 days before initial administration of drug for prostate cancer-specific antigen (PSA) evaluation and within 42 days for imaging studies; (iii) rising PSA, defined as at least two consecutive rises in PSA to be documented over a reference value (measure 1). The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure (second beyond the reference level) should be greater than the second measure, and it must be obtained at least 7 days after the second measure. If this was not the case, a fourth PSA was required to be taken and be greater than the second measure. A minimum PSA was not required. Measurable disease was also not required. However, patients who had measurable disease must have had radiographs, scans, or physical examinations used for tumor measurement completed within 28 days before the initial administration of drug. Patients must have nonmeasurable disease (such as nuclear medicine bone scans) and nontarget lesions (such as PSA level) assessed within 28 days before initial administration of drug.

Patients must have been surgically or medically castrated with medical castration continuing throughout protocol therapy and serum testosterone at castrate levels ( < 50 ng/dl) at least 3 months before registration. One (and only one) prior taxane-based chemotherapy was allowed. At least 3 weeks must have elapsed since the completion of the chemotherapy, and the patient must have recovered from the side effects of the therapy. If the patient has been treated with nonsteroidal antiandrogens (such as flutamide, bicalutamide or nilutamide) or other hormonal treatments (such as ketoconazole), these agents must have been stopped at least 28 days before enrollment for flutamide or ketoconazole, and at least 42 days before enrollment for bicalutamide or nilutamide; and the patients must have demonstrated progression of disease since the agents were suspended. Patients were required to have a Zubrod performance status of 0–2 and normal end-organ (hepatic, renal) and marrow function, determined within 14 days of registration. Concurrent bisphosphonate therapy was allowed. Patients must have agreed to use adequate contraception (hormonal or barrier method of birth control; abstinence) before study entry and for the duration of study participation. All patients were to have the ability to understand and the willingness to sign a written informed consent document before study entry.

Patients who had had chemotherapy or radiotherapy within 3 weeks before entering the study or those who had not recovered from adverse events because of agents administered for more than 4 weeks before the study were excluded. Use of specifically prohibited CYP3A4-active agents or substances was not permitted during protocol treatment, and patients who had to continue treatment with these agents were deemed ineligible. Patients with brain metastases, uncontrolled intercurrent

illness, and HIV-positive patients on combination antiretroviral drugs were also excluded.

### Treatment plan

Patients were treated with AZD0530 administered at 175 mg per day (one 125-mg tablet plus one 50-mg tablet) orally continuously. AZD0530 was to be taken at approximately the same time each morning, either 1 h before or 2 h after eating. The tablets were not to be chewed, crushed, or broken. Cycle length was arbitrarily defined as 4 weeks. Toxicities were assessed using the National Cancer Institute's Common Toxicity Criteria (version 3). In the absence of unacceptable toxicity or clear clinical progression, the patient received a minimum of two cycles of treatment. When a patient developed progressive disease after two cycles of therapy, that patient was removed from the protocol. In the absence of progression, the patient continued on protocol until unacceptable toxicity or other reason for discontinuation occurred. Criteria for removal from protocol therapy included progression of disease, unacceptable toxicity, withdrawal of patient consent, and delay of treatment greater than 4 weeks from the planned date of therapy because of toxicity.

### Response assessment

Response was assessed using Response Evaluation Criteria in Solid Tumors, which were modified to incorporate consensus recommendations on assessing response by PSA levels. All disease must have been assessed using the same technique as baseline. Complete response was defined as 'complete disappearance of all measurable and nonmeasurable disease with no new lesions, no disease related symptoms, normalization of markers and other abnormal lab values, and PSA less than 0.2 ng/ml'. Partial response was defined by either of two sets of criteria: (i) greater than or equal to 30% decrease under baseline of the sum of longest diameters of all target measurable lesions, with no new lesions, and no unequivocal progression of nonmeasurable disease; or (ii) a decline in PSA by at least 30%, confirmed by a second PSA value 4 or more weeks later with the reference PSA for these declines being a PSA measured within 3 weeks before starting therapy and patients not showing clinical or radiographic evidence of progression of measurable or nonmeasurable disease during this time period. Stable disease was defined as not qualifying for complete response, partial response, progression, or symptomatic deterioration. Progressive disease was noted when one or more of the following occurred: (i) 20% increase in the sum of longest diameters of target measurable lesions over the smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline; (ii) increase in PSA by at least 25% (by at least 5 ng/ml) over baseline; (iii) unequivocal progression of nonmeasurable disease in the opinion of the treating physician; (iv) appearance of any new lesion/site; or (v) death because of disease without prior documentation of progression and without symptomatic deterioration. Symptomatic deterioration was defined as global deterioration of health status requiring discontinuation of treatment without objective evidence of progression.

### Statistical considerations

The primary endpoint for this trial was PSA response rate. A 30% reduction in the PSA level from baseline was to be considered a favorable outcome. A 30% reduction was selected as the principal response discriminant instead of 50% as per the 1999 consensus criteria [18] because of recent data from the SWOG 9916 trial of docetaxel/estramustine versus mitoxantrone/prednisone showing that it was the 30% level which met Prentice's criteria for survival surrogacy [19]. However, patients experiencing a greater than or equal to 50% reduction in PSA level, as per consensus criteria, were also recorded in the database. A response rate of 15% after treatment with AZD0530 alone would be considered evidence of activity and encouraging of further study, whereas a response rate of less than 2% would be considered uninteresting as a single agent unless the secondary endpoint of progression-free survival (PFS) was encouraging. To evaluate the response rate a two-stage design was used. Patients who complete 1 cycle of therapy, or who terminate treatment for reasons of toxicity, or who progress before the completion of 1 cycle of therapy, were to be included in the analysis of response. The probability of falsely declaring a regimen with a discouraging response rate as warranting further study is 0.04 ($\alpha$) and the probability of correctly declaring the agent warranting further study was greater than 0.91 (power) based on the following design: in the first stage, 18 patients were to be accrued, and when there were no responders the study would terminate early. Otherwise accrual would proceed to 40 patients. When three or more responses were observed in the 40 patients, that would be considered evidence warranting further study of the schedule providing other factors, such as toxicity and time to progression, also appeared favorable. When fewer than three responses were observed in the 40 patients, further study of this schedule of AZD0530 would not be warranted based on the criteria of response rate. No break in accrual between stages was planned. With 40 evaluable patients, the 95% confidence interval for the response rate would have a half-width of $\pm$ 15% or less. If the primary endpoint was not encouraging, AZD0530 would still be considered promising as a single agent if PFS looked encouraging. Specifically, all patients were expected to progress (including PSA progression) without chemotherapy within 3 months [20]. For a one-sample, one-sided, 0.05-level test using the large-sample normal approximation for the distribution of the logarithm of the maximum likelihood estimator of the exponential parameter, there was 91% power to detect an improvement in median PFS to

**Table 1 Patient characteristics**

| | |
|---|---|
| Number of patients | 28 |
| Age, in years, median (range) | 67 (50–84) |
| Race/ethnicity (%) | |
| Caucasian | 26 (93) |
| Black | 2 (7) |
| Performance status (%) | |
| 0 | 16 (57) |
| 1 | 8 (29) |
| 2 | 4 (14) |
| Prior docetaxel-based therapy (%) | |
| Yes | 9 (32) |
| No | 19 (68) |

5 months from the null hypothesis that the median PFS is 3 months based on 12-month accrual and 6 months of follow-up. Parametric estimate of the median survival exceeding 4 months would have been sufficient to rule out the null hypothesis given the sample size of 40 patients. If the median PFS survival (estimate using a parametric method) was in excess of 4 months, AZD0530 would be considered promising based on this secondary endpoint.

## Results

### Patient characteristics

A total of 28 eligible patients were enrolled between August 2007 and November 2007. Accrual beyond the first-stage cutoff of 18 patients was because of rapid simultaneous accrual in this multi-institutional study. Patient characteristics are summarized in Table 1. Median age was 67 years, with a range of 50–84 years. Sixteen patients had performance status (PS) 0, eight patients had PS 1, and four patients had PS 2. Nineteen patients had received prior radiation therapy.

### Efficacy

Although five patients had slight PSA reductions, none of these were durable nor met the pre-specified PSA response criteria of greater than 30% from baseline. In one patient the PSA decreased from 81 to 67 ng/ml at cycle 3, then increased to 85 ng/ml. In another patient the PSA decreased from 997 to 906 ng/ml at cycle 1, with no additional data available. In one patient the PSA decreased from 122 to 94 ng/ml at cycle 2, then increased to 122 ng/ml. In one patient the PSA decreased from 3.8 to 2.9 ng/ml (baseline vs. cycle 2) then increased to 3.9 ng/ml at the very next assessment. Finally, in another patient the PSA decreased from 10270 to 8392 ng/ml from cycle 1 to cycle 2 but had symptomatic progression shortly thereafter, requiring protocol discontinuation. Median PFS was 8 weeks. Only three patients were progression free beyond 20 weeks with PSA levels within 50% of baseline values.

### Toxicity

Attributable toxicities exceeding common toxicity criteria grade 3 are reported in Table 2. AZD0530 was generally well tolerated, with a few moderate-to-severe toxicities. One grade 3 occurrence each of alanine transaminase, aspartate transaminase, nausea, vomiting, and lymphopenia were reported. One patient with preexisting metabolic syndrome died unexpectedly at home while on cycle 1 of therapy. No autopsy was performed. AZD0530 treatment was listed as a possible cause along with diabetes mellitus, morbid obesity, hypertension, hypercholesterolemia, and renal failure.

**Table 2 Grade 3 or worse toxicities (possibly, probably, or definitely) attributed to AZD0530**

| Toxicity | Grade | Occurrences |
|---|---|---|
| Alanine aminotransferase | 3 | 1 |
| Asparate aminotransferase | 3 | 1 |
| Nausea | 3 | 1 |
| Vomiting | 3 | 1 |
| Lymphopenia | 3 | 1 |
| Death, not associated with CTC term[a] | 5 | 1 |

CTC, common toxicity criteria.
[a]One patient died unexpectedly at home. No autopsy was performed. Treatment was listed as possible cause along with diabetes mellitus, morbid obesity, hypertension, hypercholesterolemia, and renal failure.

## Discussion

The role of Src-family kinases in prostate carcinogenesis and the transition to androgen independence has only recently been described. It has been shown by our group that Src kinase is critical for androgen-independent activation of androgen receptor pathways mediated by neuropeptides [21]. Our preclinical studies showed the involvement of both Src and the Src-substrate focal adhesion kinase in the IL-8-induced migration of the LNCaP cell line. Moreover, androgen-independent growth and cell migration of various prostate cancer cell lines are inhibited by the Src-inhibitors 4-amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazolo[3,4–d]pyrimidine (PP2) and dasatinib [22–24]. In addition, these and other studies have shown that alternative pathways (e.g. those mediating angiogenesis, cell survival, and neuroendocrine differentiation) are able to activate the androgen receptor in the milieu of androgen deprivation, effectively negating the growth inhibitory effects of that therapy [25–27]. Therefore, targeting the Src family of kinases (which modulate neurotrophic-mediated androgen receptor activation) seems to offer a unique platform on which to develop targeted therapy in advanced prostate cancer.

Despite promising preclinical data, this phase II trial of the orally bioavailable Src-kinase inhibitor AZD0530 in patients with established castration-refractory prostate cancer did not demonstrate any durable effects on PSA levels or PFS. One potential explanation for these results is that this single agent was clinically tested in a prostate cancer population that was least likely to benefit: patients with established, previously treated metastatic disease. In this heavily pretreated group, inhibition of the Src-

kinase family was likely insufficient in the face of already established alternative signaling pathways and resistance mechanisms. Instead, future investigations of this agent might be more relevantly applied to patients with substantially lower metastatic burden, such as those with biochemically recurrent prostate cancer while on androgen deprivation. In light of the anti-metastatic potential of Src-kinase inhibition, AZD0530 might also be reasonably tested in patients with even earlier stage disease (e.g. biochemical failure after definitive local therapy or in high risk patients after definitive local therapy). Studies of AZD0530 in combination with other established systemic therapies such as cytotoxic chemotherapy can also be considered.

AZD0530 also has bone-metabolism-modulating properties. It is known that inhibition or deletion of c-Src impairs the function of bone-resorbing osteoclasts and that AZD0530 modulates osteoclast homeostasis [28]. Our own group has shown that Id family genes are implicated in this pathway. In this work, Src was found to be requirement for bone morphogenetic protein-2 (BMP-2)-induced Id1 expression and promoter activity. It is known that BMP family members have critical roles in normal bone and cartilage development [29]. We have shown that Id family genes are downregulated by incubation of A549 lung carcinoma cells with AZD0530 [30]. Furthermore, Id1 transcript and protein levels were significantly reduced in a dose-dependent manner as were activated Src levels. AZD0530 and Id1 siRNA subsequently decreased cancer cell invasion, which was increased by Id1 overexpression. These and other encouraging preclinical work suggest that AZD0530 has a potential to be tested in the context of bone health in cancer patients, mediated through BMP family members, in addition to its antineoplastic properties.

In summary, AZD0530 was unable to induce durable PSA responses in this trial of pretreated patients with advanced castration-resistant prostate cancer. AZD0530 does have biologic activity against prostate cancer, as evidenced by strong preclinical evidence and perhaps transient PSA reductions in the five patients enrolled in this study. Further evaluation of AZD0530, particularly in earlier stage prostate cancer, may be warranted.

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