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ZD4054: A Specific Endothelin A Receptor Antagonist with Promising Activity in Metastatic Castration-Resistant Prostate Cancer

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Abstract

Overexpression of the endothelin A (ET_A) receptor has been found in a number of human cancer cell lines. Activation of the ET_A receptor by endothelin-1 (ET-1) promotes cell proliferation and survival in these tumors, whereas activation of the endothelin B (ET_B) receptor results in an opposing effect. Therefore, blockade of ET_A may have antitumor effects, while sparing ET_B-mediated effects such as induction of apoptosis and clearance of ET-1. ZD4054 is an orally bioavailable, specific ET_A antagonist currently being investigated in prostate cancer. In receptor-binding studies, ZD4054 only bound to ET_A with no binding detected towards ET_B. Prostate cancer cell lines are known to produce ET-1 and there is a relative increase in expression of ET_A to ET_B in these cancers. There is also an association of greater ET_A expression in higher grade versus lower grade tumors, suggesting that ET_A may be involved in the malignant transformation process. Since ET-1 may also mediate nociceptive effects and osteoblastic effects, there is much interest in clinically assessing ZD4054 in prostate cancer.

Keywords

Prostate cancer; endothelin receptor antagonist; osteoblast; bone metastasis

1. Introduction

Prostate cancer is the most common solid malignancy in men. It is estimated to be diagnosed in approximately 186,320 men, resulting in 28,660 deaths, in the United States in 2008 alone 1. While androgen-deprivation therapy is the mainstay of treatment in those with advanced disease, eventually all patients will develop castrate-resistant prostate cancer (CRPC), Mitoxantrone with prednisone was approved by the Food and Drug Administration (FDA) in 1996 for men with metastatic CRPC, based on an improvement in pain and quality of life (QOL) parameters, with no difference in overall survival observed 2· 3. Docetaxel and prednisone are currently the standard of care for patients with metastatic CRPC, and was FDA approved based on a statistically significant improvement in median survival of 2 – 2.5 months over mitoxantrone chemotherapy 4. While many may not consider this a giant leap forward, it does represent a new standard in this disease, against which future drugs will be judged. As a result, the approval of docetaxel-based chemotherapy has changed the current

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drug development strategies in metastatic CRPC to focus on either the pre-chemotherapy (pre-docetaxel) population, front-line chemotherapy, assessing newer agents in combination with docetaxel, or the post-docetaxel population in which no standard exists. Depending on which population is being targeted, an appropriate benchmark for drug activity success will need to be chosen based on the drug's mechanism of action, goals of therapy, as well as acceptance by regulatory bodies.

Metastatic prostate cancer is associated with significant morbidity, as it results in the development of osteoblastic bony metastases⁵. This can be accompanied by pain, increased fracture risk, and a general decrease in QOL³. In addition, hematological complications and neurologic compromise can occur, adding to the morbidity of this disease. Management of osseous tumor involvement is necessary. Androgen-deprivation therapy (ADT) is a temporary measure, but will accelerate osteoporosis, potentially increasing skeletal events^{6, 7}. Bisphosphonates, which inhibit osteoclast activity, have been shown to decrease pain and musculoskeletal events in men with osseous metastasis⁸.

While there is great need for newer therapies in CRPC, the road ahead is not well marked. Although the gold standard for drug development is showing a survival improvement, limitations include difficulties showing survival differences early in the disease course as well as in the pre-taxane state, due to the heterogeneity of disease as well as competing mortality in this older population⁹. In addition, the traditional reliance on changes in objective disease response is problematic in a disease manifesting primarily with bony metastasis¹⁰. As a result, we have become overly dependent on changes in the prostate specific antigen (PSA), which we are beginning to learn may not always correlate with clinical benefit or survival^{11, 12}.

Recent advances in the understanding of prostate cancer biology and its progression to bone metastasis have led to the development of drugs that target specific molecular alterations in the prostate tumor cell, host environment and bone. Targeting specific pathways to inhibit cancer growth, proliferation, and metastasis may be less toxic and better tolerated than conventional cytotoxic chemotherapies. The endothelin axis and its receptor-signaling pathway, is one such target that may be particularly relevant in prostate cancer, and drugs that antagonize this pathway, specifically ZD4054 is the subject of this review.

2. Endothelin and its role in prostate cancer

2.1 Endothelin Biology

The endothelins (ETs) are a family of three 21 amino acid peptides: ET-1, -2, and -3. Widely expressed in mammalian cells, they exert autocrine effects through cell-surface receptors to influence normal cellular processes involving maintenance of vasomotor tone, cellular proliferation, tissue repair and development. A number of disease states, such as hypertension (systemic and pulmonary), congestive heart failure, asthma, post-ischemic renal failure, and cerebral vasospasm, as well as neoplasia, are contributed, in part, by the dysregulation of these receptors and signaling pathways^{13–19}.

2.2 Pathophysiology of endothelin

2.2.1 The endothelin axis—The endothelin axis initiates with large pro-peptides (preproendothelins) in tissues, and undergo a two-step enzymatic cleavage to ETs. The ETs are expressed differentially depending on the tissue type. ET-1, which is not organ specific, is expressed predominantly in endothelial, epithelial, and smooth muscle cells. ET-2 is primarily found in the kidney and intestine. Lastly, ET-3 is mainly seen in the brain, intestine, lung and kidney^{14, 19}. The ETs transmit their actions through two G-protein membrane receptors, ET_A and ET_B. ET_A has a ten-fold affinity for ET-1 and ET-2 over

ET-3, and is the major effector of the ET axis. ET_B has equal affinity for all three ETs^{13–15, 18, 19}. The differential expression and activation of ET_A and ET_B in tissues determines the eventual effect that the endothelin axis exerts on the cells^{13, 14, 19, 20}.

2.2.2 Endothelin signal cascade in carcinogenesis—The ET-1/ET_A signaling cascade is the main endothelin interaction implicated in carcinogenesis. ET-1 activates ET_A via an intracellular G-protein, triggering several cellular signaling pathways (see Figure 1). This cascade leads to the activation of phospholipase C (PLC) and protein kinase C (PKC) resulting in increased levels of intracellular calcium stores^{14, 15, 21}. In addition, activation of the RAS/MAPK pathway occurs through phosphorylation of epidermal growth factor receptor (EGFR) tyrosine kinase^{22, 23}. Together, the activation of MAPK and PKC pathways, combined with increased intracellular calcium level, leads to the induction of protooncogenes, such as c-MYC, c-FOS, and c-JUN and hence stimulates cellular growth and mitogenesis^{23, 24}. Finally, ET-1 has a negative regulatory effect on apoptosis. These effects are dependant upon activation of phosphatidylinositol-3-kinase (PI3-K) and Akt protein kinase pathways. Pretreatment of cells with a selective ET_A receptor antagonist has been shown to reverse the anti-apoptotic effects of ET-1, implicating the ET-1/ET_A interaction as a survival mechanism in cancer progression^{25, 26}.

2.3 Role of endothelin and the ET_A receptor in cancer

2.3.1 Expression in cancer cells—ETs and their receptors ET_{A/B} are expressed in several cancer cell lines and tumor types¹³ including cancers of the prostate²⁷, ovary²⁸, cervix^{29, 30}, breast³¹, melanocytes³², kidney, lung, colon, central nervous system, and Kaposi's sarcoma¹³. ET_A receptors are present in high density throughout the prostate gland, and seminal fluid contains the highest concentrations of ET-1, with concentrations near 500 times that of plasma²⁷. Increased ET_A expression correlates significantly with increased tumor stage and aggressiveness^{33, 34}. Conversely, ET_B appears to be down-regulated in the presence of cancer. Though ET_B binding sites are found on benign prostatic tissue, they are much reduced or absent in metastatic prostate cancer^{20, 35}. ET_B counter-regulates ET-1/ET_A activity through a variety of mechanisms: 1) it increases production of nitrous oxide, thus counteracting ET_A ET -induced calcium-dependant vasoconstriction; 2) provokes apoptotic pathways, balancing the cell growth and survival pathways of ET; 3) it directly incites clearance of ET-1; and 4) it may inhibit secretion of ET-1^{20, 34, 35}.

The balance of ET_A and ET_B activation in tumor cells appears to be important in the progression of most cancers²¹, especially prostate cancer³⁶, contributing to increased tumor cell survival and growth.

2.3.2 Cell growth and survival—There is accumulating evidence to suggest activation of ET_A by ET-1 has a role in regulating growth and proliferation of tumors¹⁷. ET-1 induces DNA synthesis and cell proliferation in numerous cells, including osteoblast, fibroblast, prostatic smooth muscle and epithelium and prostate cancers^{27, 36, 37}. In vitro, the activity of ET-1 in prostate cancer is demonstrated by the induced proliferation of all prostate cancer cell lines by exogenous ET-1²⁷. In preclinical studies, selective ET_A receptor antagonist, ZD4054, specifically inhibited ET_A mediated anti-apoptotic effects on human smooth muscle cells.^{38, 39}

The binding of ET-1 to ET_A and ET_B causes distinct and opposing effects on cell growth and survival (see Figure 1). In most cells, activation of ET_A promotes cell growth¹⁷, while activation of ET_B induces apoptosis⁴⁰. Therefore selective targeting of ET_A may be useful in the treatment of prostate cancer

2.3.3 Angiogenesis in the malignant process—ET-1 and ET_A have been linked to neovascularization in both tumor and the surrounding environment³⁶. Activation of ET_A by ET-1 modulates the production of vascular endothelin growth factor (VEGF), which can promote angiogenesis, in part by inducing hypoxia-inducible factor-1, promoting endothelial cell proliferation and enhancing vascular permeability^{17, 41–44}. VEGF is overexpressed in many tumors, including prostate cancer. *In vivo*, the combination of ET-1 and VEGF produce significantly more angiogenesis than either alone^{45, 46}.

2.3.4 Spread and development of bone metastasis—The activation of ET_A by ET-1 upregulates tumor proteases (matrix metalloproteinases) and urokinase-type plasminogen activator⁴⁷. These mechanisms of invasion and migration are inhibited when ET-1 is blocked by ET_A-selective receptor antagonists^{47–49}.

Additionally, activation of ET_A by ET-1 leads to proliferation of osteoblasts, bone remodeling and release of growth factors that stimulate survival and growth of metastatic^{50–52} tumor cells within osseous metastasis^{53, 54}. ET-1 has also been shown to stimulate mitogenesis in the osteoblast and, at the same time, decrease osteoclastic bone resorption and motility⁵³. Studies have demonstrated ET-1 stimulation increased alkaline phosphatases activity, suggesting an osteoblastic response²⁷. Prostate cancer cell lines co-cultured with bone slices had increased levels of ET-1 and inhibited osteoclastic bone resorption. This effect was negated by the addition of a specific anti-ET-1 antibody^{37, 53, 55}. In pre-clinical studies, selective endothelin A receptor antagonist, ZD4054, was shown to block ET_A-mediated activation of p44/42 mitogen-activated protein kinase in murine osteoblast cells and inhibit ET-1 induced proliferation of human immature pre-osteoblast cells.⁵⁶

2.3.5 Role in the nociceptive response—Human subjects injected with ET-1 experience intense dose-dependant pain; this pain can be reduced on administration of an ET_A receptor antagonists⁵⁷. High levels of ET-1 are found in dorsal root ganglion and ET_A receptors can be found on small to medium sized root ganglion neurons and their axons⁵⁸. Through a recently defined intrinsic feedback mechanism, ET-1 is able to trigger pain by stimulating the ET_A receptors located in the root ganglion neurons. Conversely, ET-1 activation of ET_B produces an anti-nociceptive or analgesic effect by the release of β -endorphin⁵⁹. Selective inhibition of ET_A markedly reduces the ET-1 stimulated pain response while preserving the favorable anti-nociceptive or analgesic effects of ET_B activation⁶⁰.

In summary, numerous studies implicate the ET-1/ET_A interaction as a pivotal player in cancer cell signaling pathways, growth, proliferation, avoidance of apoptosis, invasion, angiogenesis, metastasis (particularly to bone) and the propagation of pain. All of which are inhibited by the use of selective ET_A receptor antagonists, while retaining beneficial ET_B receptor mediated effects such as apoptosis and clearance of ET-1 and antinociceptive or analgesic activity.

3. Endothelin antagonists in cancer therapy

3.1 Endothelin antagonists

There are several endothelin antagonists which have been actively studied for cancer treatment in clinical trials. These drugs selectively target ET_A over ET_B, but in varying degrees.

YM598 (Astellas Pharma Inc.) is a highly selective ET_A antagonist that is 816-fold more selective for the ET_A receptor than ET_B (K_i = 0.697 and 569nM (n=6) for ET_A and ET_B respectively)⁶¹. YM598 has been combined with mitoxantrone and prednisone in a

randomized, double-blind, placebo-controlled phase II trial to assess benefits in cancer related pain in men with metastatic CRPC. However, this trial was terminated early due to lack of efficacy.

Atrasentan (ABT-627; Xinlay: Abbott Laboratories). It is an orally bioavailable, selective ET_A receptor inhibitor (K_i = .069 and 138.6 nM (n=3) for ET_A and ET_B. IC₅₀ = 0.11 nM and 98.2nM (n=5) for ET_A and ET_B) - more than 2000 times more selective for ET_A over ET_B⁶². In phase I studies it was found to have good tolerability and safety in a diverse population.

Several phase II trials have been conducted evaluating Atrasentan in men with CRPC. The first assessed pain relief and changes in bone markers in men with metastatic CRPC requiring opioids. The second assessed time to clinical progression in asymptomatic men with metastatic CRPC. Though both trials showed positive trends, their primary endpoints were not statistically significant^{63, 64}. A third study combined Atrasentan with zoledronic acid in men with metastatic prostate cancer. This trial too failed to demonstrate its primary endpoint of bone marker improvement⁶⁵.

In a phase III, multinational, double-blind, randomized, placebo-controlled trial of 809 men with metastatic CRPC, despite encouraging trends, its primary endpoint of time to disease progression did not reach statistical significance⁶⁶.

A current phase III trial combining Atrasentan and Taxotere in patients with advanced CRPC is ongoing and we await its results upon completion.

While each of these studies had numerous challenges and failed to reach their primary endpoints, they contribute largely to the accumulating and consistent data of endothelin antagonist research and offer information for future trial designs.

4. ZD4054

4.1 Pharmacology

4.1.1 Chemical name, structure and properties—ZD4054, chemically designated as N-(3-Methoxy-5-niethylpyrazine-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide is a crystalline solid with two measurable pK_a values at 1.46 and 5.66 (see Figure 2). It is soluble in distilled water (0.12mg/ml at 25 Celsius). The molecular weight is 424.4.⁶⁷

4.1.2 Receptor specificity—Of the orally available endothelin receptor antagonists, ZD4054 most potently and selectively binds ET_A over ET_B. In multi-receptor binding screens the mean K_i values measured were 13nM and mean pIC₅₀ values were 21 nM. In contrast, ZD4054 had no measurable affinity for cloned human ET_B. In the same multi-receptor binding screens ZD4054 was inactive at ET_B at a concentration of >10μM.⁵⁴

4.1.3 Distribution and metabolism—In studies of [¹⁴C]-ZD4054 in healthy volunteers reported by Clarkson-Jones, et al show radioactivity in whole blood was generally less than in plasma and mean plasma protein binding level was 73%. This suggests a limited association of drug-related material with blood cells and is unlikely to be affected by co-medication with other drugs, at least as consequence of protein binding displacement interactions⁶⁸.

Concentrations of ZD4054 were similar to total radioactivity until 12 hours post dose, after which concentrations of radioactivity were slightly higher than ZD4054, indicating the

presence of circulating metabolites. P6 (hydroxide) was the only detectable metabolite, accounting 4% of plasma radioactivity and no other metabolites were detected after 24 hours⁶⁸.

There were similar metabolite profiles for urine and feces samples. The main metabolites in urine and feces were P3 (despyrazine), P4 (hydroxylated pyrazine), P6 (hydroxide) and P3, P4, respectively. Overall recoveries of radioactivity were high, ranging from 81–99% (mean 93.4%). Excretion via the urine was rapid and extensive: recoveries ranged from 71–94% of the dose, with mean renal clearance of ZD4054 calculated at 1.1 liter/hour. Renal clearance contributes significantly to the overall clearance of ZD4054⁶⁸.

Preclinical results indicate that ZD4054 is metabolized via the cytochrome P450 system using isozyme 3A4 (Cyp3A4). A study was designed to evaluate the effect of a potent CYP3A4 inducer and CYP3A4 inhibitor on the pharmacokinetics and metabolism of ZD4054⁶⁹. This trial showed that ZD4054 15mg given to healthy volunteers predosed with rifampicin 600mg reduced the C_{max} and the AUC of ZD4054 by 29 and 68%, respectively. Rifampicin also reduced the $t_{1/2}$ from 8.2 to 2.7 hours, while the t_{max} did not seem to be affected. This suggests that CYP3A4-inducing drugs may reduce the efficacy of ZD4054. Conversely, in volunteers receiving ZD4054 10mg predosed with CYP3A4 inhibitor itraconazole increased the C_{max} and AUC of ZD4054 by 29 and 27%, respectively. This is a small increase of ZD4054 exposure and effect that is unlikely to significantly alter the safety profile⁶⁹.

4.2 Clinical development of ZD4054

4.2.1 Pharmacokinetics—Pharmacokinetics of ZD4054 has been studied in both healthy volunteers and patients^{68, 70}. Single dosing of 15mg ZD4054 was rapidly absorbed with peak plasma concentrations (C_{max}) observed in 1–3 hours after dosing and exposure increased with dose^{68, 70}. Plasma concentrations declined in a monophasic manner and the mean half-life was between 9–12 hours⁷⁰.

In multiple dose kinetics studies there was minimal accumulation of ZD4054 after 4 or 5 daily consecutive doses. AUC_{0–24} values on day 15 were generally in accordance with predicted values from the single dose data⁷⁰.

In studies comparing between ethnic groups of Caucasian and Japanese patients there were no marked differences in the C_{max} and AUC_{0–24} in either single or multiple dosing schedules. In Japanese patients who received ZD4054 15mg (single or multiple dose), some patients achieved higher exposure than Caucasian counterparts, but these differences disappeared when the data were normalized for the body weights of the patients⁷⁰.

4.2.3 Clinical Safety—Safety and tolerability profiles remain consistent throughout a number of clinical trials^{69–71}. In a phase IIa, open-label, multi-center dose-escalation study the starting dose was 10mg and doses were escalated to 15mg and 22.5mg⁷¹. The therapy was well tolerated. Dose limiting toxicities were encountered at 22.5mg with dyspnea, peripheral edema, headache and intraventricular hemorrhage. At 15mg, no dose limiting toxicities were seen. Secondary to vasodilation and fluid retention, the most frequent adverse events at 15mg were headache, peripheral edema, fatigue, nasal congestion and nausea. Mild weight gain (0.7kg) and decrease in hemoglobin of 0.8mg/dl (from hemodilution) were also observed. These events were reversible upon drug cessation. This observed tolerability profile is consistent with effects rising from specific ETA antagonism⁷¹.

4.2.4 Efficacy of ZD4054: phase II prostate cancer study data—ZD4054 was further studied in a multi-center phase II, randomized, double blind, placebo-controlled trial. A total of 312 asymptomatic or mildly symptomatic CRPC patients with bone metastasis were randomized into one of three treatment arms: 15mg ZD4054 once daily; 10mg ZD4054 once daily or a placebo tablet. The primary end point of the study was progression free survival (PFS) and a secondary endpoint was overall survival (OS). While the PFS data did not show a statistically significant difference between ZD4054 and placebo treatment arms, preliminary survival data suggested an improvement in OS. Patients who received ZD4054 10mg once daily experienced a 45% reduction in the risk of death compared with placebo (HR 0.55; 80% CI 0.41, 0.73), translating into an improved median OS of 24.5 months with ZD4054 10mg once-daily compared with 17.3 months in the placebo arm.

Patients who received ZD4054 15mg once-daily experienced a 35% reduction in the risk of death (HR 0.65; 80 CI 0.49, 0.86), again translating into an improved median OS of 23.5 months with ZD4054 15mg once daily compared with 17.3 months in the placebo arm ^{72, 73}.

4.2.5 Efficacy of ZD4054: phase III prostate cancer study data—Currently, there are 3 phase III trials conducted as part of a program known as Endothelin A Use (ETHUSE). All of the trials will use a once daily dose of ZD4054 at 10mg. The first is a large phase III study of the safety and efficacy of ZD4054 vs. placebo in patients with CRPC and bone metastases. The primary outcomes focus on overall survival. The second trial tests the efficacy of ZD4054 vs. placebo in men with CRPC without evidence of metastases, but have rising PSA values. The primary outcomes are overall survival and progression free survival. Lastly, the third of the phase III trials combines ZD4054 with docetaxel in men with non-metastatic CRPC. The primary outcome in this study is overall survival.

Conclusion

For many patients with CRPC chemotherapy may not be a viable or desirable treatment option. Therefore, targeting the endothelin axis offers a new and promising approach in the treatment of CRPC. There is considerable preclinical data suggesting that the activation of the ET_A receptor by ET-1 promotes prostate cancer growth, bone metastasis and pain. Drugs such ZD4054 have been shown to specifically block ET_A with high affinity while sparing the ET_B receptor⁵⁴. Phase II clinical trials demonstrate its safety and tolerability in patients with CRPC, with suggestions that ZD4054 may be beneficial in patients with asymptomatic or mildly symptomatic metastatic CRPC by improving overall survival⁷². These results offer the impetus for further trials. Phase III studies with ZD4054 are planned in CRPC, administered either as monotherapy or in combination with chemotherapy, with overall survival as the primary endpoint.

Expert opinion

Metastases to bone are the principal cause of morbidity and mortality in prostate cancer. This is an ongoing challenge not only for the clinical management of prostate cancer, but also prostate cancer drug development, as current imaging modalities are not capable of assessing response in osseous metastasis with certainty ⁷⁴. As a result, we have necessitated that differences in survival be the prerequisite for prostate cancer drug approval. While reducing mortality from prostate cancer is the stated goal, the reduction of morbidity from prostate cancer should be considered of equal importance. The scientific rationale for use of endothelin receptor antagonists in prostate cancer is unique in that it may address both of these issues simultaneously. The finding of over-expressed ET_A receptors on prostate cancers with elevated circulating ET-1 levels in men with prostate cancer strongly suggests

that the endothelin axis is important in prostate cancer proliferation and survival. Likewise, the finding that ET-1 activity induces osteoblastic and osteoclastic responses in bone strongly suggest that there is a synergistic feedback loop between the prostate cancer cells and osteoblasts/osteoclasts, which facilitates the propagation of the tumor in bone. Early clinical trials with the ET_A antagonist atrasentan 63 did suggest improvements in time to progression in patients with prostate cancer and osseous metastasis 66, as well as improvements in bone pain⁴¹ supporting the importance of the endothelin axis in prostate cancer. Unfortunately, these trials failed to show a statistically significant improvement in time to progression (as defined in the protocol) resulting in the FDA's recommendation not to approve atrasentan. ZD4054 is a specific ET_A receptor antagonist currently being investigated in prostate cancer. Learning from the protocol failures seen with atrasentan, the randomized, placebo-controlled study of ZD4054 was powered to show a progression free survival improvement, but was more careful in defining progression with a composite endpoint. This included clinically meaningful endpoints such as clinical progression, pain requiring opioids, progressive soft tissue metastasis, and death, but excluded clinically controversial endpoints such as PSA or bone scan worsening. Although no statistical difference in progression free survival was observed, an improvement in overall survival was seen with ZD4054 versus placebo. We expect that improvements in PFS lead to improvements in overall survival and have, as a prostate research community, been encouraging our regulating bodies to accept PFS as an appropriate surrogate (such as in breast cancer) to facilitate drug development, especially as we treat patients earlier in their disease course (pre-docetaxel). How does one account for the improvement in overall survival without a difference observed in PFS with ZD4054? One possible conclusion is that the study was underpowered to show an overall survival difference, and thus this observed difference could be due to chance alone. Another is that the benefit in terms of improving PFS may be more appreciable in patients without established osseous metastasis, and that in the presence of established osseous metastasis, the benefit (including survival) of ZD4054 might be due to its palliative effects. In general, we need to take into account several factors: 1) the expected action for the drug on the cancer (cytostatic or cytotoxic), 2) the goals of therapy (curative, prolongation of life, palliative), and 3) the disease state being assessed (e.g. rising PSA only, pre-docetaxel, in combination with docetaxel, or taxane-refractory), when designing clinical trial endpoints. Moving forward, the most clinically meaningful endpoint might be improvements in time to radiographic progression (rising PSA state), survival (metastatic, pre-docetaxel state), or pain improvement (post-docetaxel state).

Further investigation of ZD4054 in prostate cancer is warranted, and Phase III trials are already planned in patients with non-metastatic CRPC with rising PSA values, metastatic (asymptomatic) CRPC, and in metastatic CRPC in combination with docetaxel, assessing either differences in PFS and OS or OS alone. We must keep in mind that the ultimate objective is to reduce the mortality and morbidity from prostate cancer. What this implies is that although survival improvement is important, it represents only one half of the goal.

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Figure 1.

Shown is the endothelin axis and cascade. Activation of endothelin receptor A (ET_A) by endothelin-1 (ET-1) leads to increased cell proliferation and survival. Activation of endothelin receptor B (ET_B) by ET-1 facilitates cell apoptosis and results in decreased levels endothelin-1 (ET-1).

Figure 2.
Chemical structure of ZD4054