# Dose-escalated abarelix in androgen-independent prostate cancer: a phase I study

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**Follicle-stimulating hormone has been shown to be a mitogen in preclinical models of androgen-independent prostate cancer and abarelix has been previously shown to significantly reduce follicle-stimulating hormone levels in patients when administered monthly. Consequently, we evaluated the safety of more frequent (biweekly) dosing of abarelix and characterized the effect of this dosing schedule on serum follicle-stimulating hormone levels in men with prostate cancer that is progressing despite luteinizing hormone-releasing hormone agonist therapy. Twenty-one patients with prostate cancer progressing on gonadotropin-releasing hormone agonist therapy discontinued the gonadotropin-releasing hormone agonist and received abarelix-depot 100 mg by intramuscular injection every 2 weeks for up to 12 weeks. Safety profile and effect on serum follicle-stimulating hormone were the primary end-points, while prostate-specific antigen response was a secondary end-point. Abarelix therapy was generally well tolerated. One patient experienced an acute immediate allergic reaction. The mean follicle-stimulating hormone serum concentration declined from 3.5 mIU/ml (95% confidence interval: 2.7–4.3) to 2.0 mIU/ml (95% confidence interval: 1.3–2.6) on day 57 and to 2.0 mIU/ml (95% confidence interval: 0.9–3.0) on day 85 ($P=0.008$ in a Kruskal–Wallis test), but no patient's follicle-stimulating hormone has reached the lower limit of quantitation (below 0.15 mIU/ml). No patient met criteria for prostate-specific antigen response. At the end of 12 weeks of therapy, three (14.3%) patients had no change in prostate-specific antigen levels on days 57 and 85 compared with baseline. Twelve patients (57%) had stable disease throughout treatment defined as percent change from baseline within −50 to 50% at a given time-point confirmed by a second measurement at least 4 weeks later. Treatment with biweekly abarelix in patients with androgen-independent prostate cancer is feasible with no unexpected toxicity, but fails to completely suppress serum follicle-stimulating hormone levels or produce prostate-specific antigen responses.** ***Anti-Cancer Drugs*** **17:1075–1079 © 2006 Lippincott Williams & Wilkins.**

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## Introduction

Preclinical evidence suggests that follicle-stimulating hormone (FSH) may contribute to the progression of androgen-independent prostate cancer (AIPC). FSH receptor is expressed in both cell lines and human specimens of prostate cancer [1,2]. FSH receptor expression has been shown in primary culture to be greater in malignant than in benign prostate tissue [2]. Benign and malignant epithelial cells from the prostate have been shown to produce FSH [1,2]. FSH stimulates proliferation and diminishes apoptosis in androgen-independent PC-3 cells *in vitro* [2]. Therefore, both autocrine and paracrine mechanisms of FSH may play a role in prostate cancer proliferation.

Studies in healthy volunteers have shown that luteinizing hormone (LH) is sustainably suppressed when participants were treated with LH-releasing hormone (LHRH) agonists. In contrast, FSH levels reached a nadir of about 30% of pretreatment value between weeks 1 and 4, and partially escaped from suppression shortly after reaching the nadir [3]. Prostate cancer patients being treated with LHRH agonists have shown a similar escape [4–6]. On the basis of preclinical data and clinical observations that show persistent circulating FSH levels in patients on standard hormonal therapy, we postulated that circulating FSH may contribute to the progression of AIPC.

Unlike LHRH agonists, gonadotropin-releasing hormone (GnRH) antagonists significantly reduce circulating FSH. In a phase II study, Garnick *et al.* reported that men initiating hormonal therapy with the GnRH antagonist abarelix-depot had FSH levels that were sustainably suppressed. Throughout an 85-day observation period, the median FSH concentration remained below 3.0 IU/l, whereas a matched group of patients treated with an

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LHRH agonist with or without androgen receptor antagonists experienced a nadir median FSH concentration of 4.9 IU/l after 3 weeks of therapy followed by a rise to a median of 11.1 IU/l by the end of 85 days [7].

Our group reported that abarelix further suppressed FSH in 20 patients whose cancer was progressing on LHRH agonist therapy. Median FSH declined from 4.9 to 2.4 IU/l after 4 weeks and to 2.0 IU/l after 8 weeks. No patients, however, met the primary efficacy end-point of a confirmed 50% reduction in the prostate-specific antigen (PSA) [8].

The current dosing regimen of abarelix was not specifically designed to maximally suppress circulating FSH. Rather, it was developed to suppress testosterone in the initial hormonal management of prostate cancer. While we previously demonstrated that the standard dose and schedule of abarelix does significantly reduce the circulating concentrations of FSH when used in the second-line hormonal therapy setting, we did not attain complete suppression of FSH and did not see clinical responses using this dosing schedule. We hypothesized that a higher dose intensity of abarelix may more completely suppress serum FSH and consequently may lead to clinical responses in patients progressing on a GnRH agonist.

## Methods

### Patients

Eligible patients had histologically or cytologically confirmed prostate cancer progressing despite LHRH agonist therapy with a demonstrated castrate serum testosterone concentration. Progression was defined as a rise in the PSA confirmed by two measurements at least 2 weeks apart, or the appearance of new metastatic lesions, or progression of known metastatic lesions. Progression had to be demonstrated after withdrawal of androgen receptor antagonists (6 weeks for bicalutamide, 4 weeks for flutamide or nilutamide) in patients receiving combined androgen blockade. Other requirements included: Eastern Clinical Oncology Group performance status $\leq 3$, age $\geq 18$ years of age, serum testosterone $\leq 50$ ng/dl, PSA $\geq 5$ ng/ml, white blood cells $\geq 3000/mm^3$, hematocrit $\geq 30\%$, platelet count $\geq 100\,000/mm^3$, serum creatinine $\leq 2 \times$ upper limits of normal (ULN), bilirubin (direct or total) $\leq 2 \times$ ULN, SGPT (alanine aminotransferase) and SGOT (aspartate aminotransferase) $\leq 2 \times$ ULN.

Prior treatment for prostate cancer with chemotherapy, radiopharmaceuticals, diethylstilbesterol or another estrogen, PC-SPES, ketoconazole or aminoglutethamide was not allowed. Concurrent treatment with class IA or class III antiarrhythmic medications was prohibited. Patients were also excluded for: allergy to an LHRH agonist or antagonist, any uncontrolled infection, including HIV, major surgery within 4 weeks, serious medical illnesses, NYHA class III or IV congestive heart failure, unstable angina within 6 months, myocardial infarction within 12 months, acute deep venous thrombosis within 2 years, any history of acute pulmonary embolism, QTc $> 450$ ms on screening electrocardiogram (ECG) or active second malignancy other than nonmelanoma skin cancer (patients in remission who had a $> 30\%$ risk for relapse were considered to have an active malignancy).

The protocol was approved by the Institutional Review Boards at all participating institutions. Written informed consent was obtained from all patients.

### Objectives

The primary end-points of the study were to evaluate the safety of biweekly dosing of abarelix and the effect of abarelix on serum FSH. Efficacy end-points related to serum FSH were percent change from baseline in serum FSH on days 57 and 85 and percent of patients with FSH below or at the lower limit of quantitation (LLOQ) on days 57 and 85. The secondary end-points were to evaluate the effect of abarelix on serum testosterone, LH and to determine whether biweekly abarelix has clinical activity in AIPC as measured by PSA responses (50% reduction confirmed 4 weeks later). Serum abarelix concentrations as well as changes in bone pain and use of narcotic analgesia from baseline were also examined.

### Treatment

Intramuscular injections of abarelix-depot 100 mg were given every 2 weeks for up to 12 weeks (total dose of 600 mg). Patients were observed for at least 60 min after each abarelix injection.

### Monitoring

Baseline evaluation included a complete history and physical examination, complete blood count with automated differential, serum alanine aminotransferase, serum aspartate aminotransferase, alkaline phosphatase, bilirubin, creatinine, serum testosterone, FSH, LH, serum PSA, urinalysis, 12-lead ECG, radionuclide bone scan and computed tomography or magnetic resonance imaging of the abdomen and pelvis. An axial computed tomography or magnetic resonance imaging of the spine was obtained in patients with spinal metastases.

Every 2 weeks adverse events were recorded and blood was collected for serum abarelix levels. Every 4 weeks 12-lead ECG was performed, and blood was collected for hematology and clinical chemistries, serum testosterone, FSH, LH and serum PSA.

Each patient had his serum testosterone, FSH, LH and serum PSA measured in the same laboratory throughout

the study (Covance Central Laboratory Services). The LLOQ for the assays were as follows: FSH 0.15 mIU/ml, LH 0.5 mIU/ml, PSA 0.01 ng/ml and testosterone 8 ng/dl.

All toxicities were graded according to the WHO toxicity scale.

### Statistical considerations

The sample size was calculated based on safety evaluation of abarelix. If a given adverse event occurs with 10% incidence in this population, the probability is 0.90 that at least one of 22 participants will experience that event. If a given adverse event occurs with 5% incidence in this population, the probability is 0.68 that at least one of 22 participants will experience that event. A sample size of 22 participants provides the following 95% confidence interval (CI) around percentage participants with FSH $\leq$ LLOQ (Table 1)

Primary analysis population was intent-to-treat population, consisting of all eligible patients who received at least one dose of abarelix during the study.

## Results

### Patients

Twenty-one men were recruited between May 2004 and May 2005 at six US sites. Pretreatment patient characteristics are summarized in Table 2. Briefly, the median age was 72 years. The majority of patients (16; 76%) were enrolled with an Eastern Clinical Oncology Group performance status of 0. At the study entry, the median serum FSH was 3.4 mIU/ml (range: 1–18 mIU/ml) and the median PSA was 26.8 ng/ml (range: 4–1299 ng/ml). Eleven (52%) patients had metastatic disease (all limited to bony sites) and 10 (48%) patients had no radiographically detectable metastases. For the purposes of study eligibility, progression was demonstrated by PSA in 20 patients and by progression of measurable or evaluable lesions on imaging studies with or without a rising PSA only in one patient. The median follow-up for the entire study population was 90 days (range: 15–134 days). Pretreatment testosterone ranged from $<8$ to 173 ng/dl. One patient was enrolled with a baseline testosterone level of $\geq 50$ ng/dl. This patient had missed 2 months of leuprolide acetate therapy prior to study entry. This patient was included in the safety analyses, but was excluded from all efficacy analyses.

**Table 1 Exact 95% CIs for various response rates based on 22 evaluable participants**

| Participants with FSH $\leq$ LLOQ (%) | 95% CI | |
|---|---|---|
| | Lower bound | Upper bound |
| 20 | 3 | 37 |
| 40 | 19 | 61 |
| 60 | 39 | 81 |
| 80 | 63 | 97 |

CI, confidence interval; FSH follicle-stimulating hormone; LLOQ, lower limit of quantitation.

**Table 2 Patient characteristics on entry**

| | |
|---|---|
| No. of patients | 21 |
| Age (years) | |
| median (range) | 72.0 (51–87) |
| ECOG performance status | |
| 0 | 16 (76.2%) |
| 1 | 4 (19.0%) |
| 2 | 1 (4.8%) |
| FSH (mIU/ml) | |
| median (range) | 3.4 (1–18) |
| PSA (ng/ml) | |
| median (range) | 26.8 (4–1299) |
| Testosterone (ng/dl) | |
| median (range) | 11.0 (8–173) |
| LH (mIU/ml) | |
| median (range) | 0.5 (1–11) |
| Alkaline phosphatase (u/l) | |
| median (range) | 88.0 (62–366) |
| Site of metastases | |
| bone only | 11 (52) |
| none | 10 (48) |
| Prior hormonal therapy (%) | |
| combined androgen blockade | 17 (81%) |
| LHRH agonist monotherapy | 4 (19%) |

ECOG, Eastern Clinical Oncology Group; FSH, follicle-stimulating hormone; PSA, prostate-specific antigen; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone.

### Treatment

Ten patients completed the planned 12-week treatment course and 11 patients withdrew prematurely. Nine patients withdrew because of disease progression, whereas two patients withdrew because of adverse events.

### Toxicity

No deaths occurred. Treatment was generally very well tolerated. Two patients had treatment discontinued because of toxicity. One patient experienced immediate-onset of allergic reaction soon after day 15 dose, whereas the other patient withdrew because of urine retention. Three patients (14%) experienced adverse events of severe toxicity with one patient experiencing more than one severe adverse event. Toxicities are reported in Table 3.

### Abarelix levels

Mean abarelix levels were 14.7 ng/ml (95% CI: 11.8–17.6) on day 29, 21.9 ng/ml (95% CI: 15.5–28.2) on day 57 and 31.1 ng/ml (95% CI: 5.8–56.4) on day 85. As expected, mean abarelix levels, assessed prior to injection, were considerably higher on days 57 and 85 in this study than the levels observed in prior studies conducted with every 4-week dosing [7,9,10].

### Effects on serum follicle-stimulating hormone

None of the study patients achieved FSH suppression to or below the LLOQ on days 57 and 85. The LLOQ used

**Table 3 Number of patients experiencing each adverse event ($n=21$)**

| Adverse event | Mild [*n* (%)] | Moderate [*n* (%)] | Severe [*n* (%)] | Any [*n*(%)] |
|---|---|---|---|---|
| Number of patients with at least one adverse event | | | | 9 (43) |
| Anemia | 1 (5) | 0 | 1 (5) | 2 (10) |
| Bradycardia[a] | 0 | 0 | 1 (5) | 1 (5) |
| Unresponsive to verbal stimuli[a] | 0 | 0 | 1 (5) | 1 (5) |
| Hypotension[a] | 0 | 0 | 1 (5) | 1 (5) |
| Urticaria[a] | 0 | 0 | 1 (5) | 1 (5) |
| Urinary retention | 0 | 0 | 1 (5) | 1 (5) |
| Arthralgia | 1 (5) | 1 (5) | 0 | 1 (5) |
| Dizzyness/presyncope | 1 (5) | 1 (5) | 0 | 2 (10) |
| Cerbrovascular accident | 0 | 1 (5) | 0 | 1 (5) |
| Chest pain | 0 | 1 (5) | 0 | 1 (5) |
| Bone pain | 0 | 1 (5) | 0 | 1 (5) |
| Neck pain | 0 | 1 (5) | 0 | 1 (5) |
| Spondylitis | 0 | 1 (5) | 0 | 1 (5) |
| Facial palsy | 0 | 1 (5) | 0 | 1 (5) |
| Dyspnea | 0 | 1 (5) | 0 | 1 (5) |
| Epistaxis | 0 | 1 (5) | 0 | 1 (5) |
| Pleural effusion | 0 | 1 (5) | 0 | 1 (5) |

All moderate or higher events and mild events that occurred in more than one patient regardless of attribution are shown.
[a]Occurred in the same patient.

in FSH assay was 0.15 mIU/l. The median FSH declined from 3.2 mIU/l (range: 1–8) at baseline to 1.7 mIU/l (range: 0.4–5) on day 57 and 1.9 (range: 1–3) on day 85. The mean FSH concentration declined from 3.5 mIU/ml (95% CI: 2.7–4.3) to 2.0 mIU/ml (95% CI: 1.3–2.6) on day 57 and to 2.0 mIU/ml (95% CI: 0.9–3.0) on day 85 ($P = 0.008$ in a Kruskal–Wallis test). Median percent change from baseline was −44.8% (range: −72% to +8%) on day 57 and −53.9% (range: −68% to +1%) on day 85. FSH data were available for 20 patients at baseline, 17 patients on day 57 and 6 patients on day 85 in an intent-to-treat population excluding the patient with a baseline testosterone $\geq$ 50 ng/dl.

A statistically significant correlation does not exist between abarelix and FSH concentrations; however, the study was not powered to adequately examine this question.

### Effects on testosterone and luteinizing hormone

Testosterone remained suppressed below castrate levels in all patients who entered with a castrate testosterone and reached castrate levels for the one patient who entered the study with an inadequately suppressed testosterone.

Serum LH data were evaluated for 20 patients at baseline and for 17 patients on day 57 and six patients on day 85. LH levels were below quantifiable levels for all but one patient who was not chemically castrate at study entry and for all patients during on-therapy assessments.

### Effects on prostate-specific antigen and disease status

Except for one patient who was not chemically castrate with a baseline testosterone of 173 ng/dl, none of the other patients had a decline in PSA levels on days 57 and 85. At the end of 12 weeks of therapy, three (14.3%) patients had no change in PSA levels on days 57 and 85 compared with baseline. Twelve patients (57%) had stable disease throughout treatment defined as percentage change from baseline within −50 to 50% at a given time-point confirmed by a second measurement at least 4 weeks later.

### Effect on pain and narcotic use

At baseline, 10 patients reported pain. The median pain score in patients with pain was 1.3 (range 0–7). Given this relatively low level of pain at baseline, no additional analyses of pain outcomes were carried out.

## Discussion

In this study, we administered abarelix at a significantly higher dose intensity than in our previous studies. Trough abarelix concentrations measured on days 57 and 85 were considerably higher than in previous studies, as expected. The safety profile of abarelix does not appear to be measurably different from biweekly administration than has been reported with administration every 4 weeks.

Although we observed substantial reduction (approximately 50%) in serum FSH concentrations in patients in this study, the reduction in FSH concentrations was similar in magnitude to the effect we previously observed with every 4-week administration in a similar patient population [8]. Although we did not examine a broad range of abarelix doses, and it is possible that even higher doses of abarelix could suppress FSH further, this study does not provide evidence of a dose–response relationship between abarelix and FSH suppression in patients with LHRH-agonist-resistant prostate cancer.

Indeed, the study provides clinical evidence for differential secretion of FSH and LH, and suggests that while LH secretion is highly GnRH dependent and suppressible with either a GnRH agonist or antagonist, FSH secretion may not be entirely GnRH dependent. Differential secretion of LH and FSH has been a vexing problem studied by reproductive endocrinologists. A dissociation between LH and FSH levels occurs in a range of clinical situations including the luteo-follicular transition, menopausal transition, treatment with gonadal steroids and LHRH agonists [11]. This dissociation cannot be explained by differences in the plasma half-lives of LH and FSH alone [11]. While the mechanisms that underlie these observations are not fully understood, non-GnRH regulators of FSH secretion have been

described. When the pituitary gland is transplanted under the renal capsule, and therefore isolated from GnRH, LH secretion largely stops, but FSH secretion is not fully suppressed [12]. Activin, a covalently linked dimer of inhibin β-subunits, has been shown to stimulate FSH secretion independently of GnRH in in-vitro systems [13] and to increase circulating FSH *in vivo* [14].

Despite complete suppression of LH and more efficient suppression of FSH that is seen with LHRH agonists, biweekly abarelix administration appears to be no more effective in suppressing FSH than abarelix administered every 4 weeks. The residual circulating FSH levels observed in the patients in this study may represent the GnRH-independent portion of FSH secretion in men.

As we were unable to fully suppress FSH in this study, we could not test our hypothesis that suppressing FSH signaling would produce disease responses in AIPC. This hypothesis remains intriguing in view of the strongly supportive preclinical data. Thus, the FSH signaling pathway remains an interesting therapeutic target in prostate cancer. Drugs that target the FSH receptor directly or target non-GnRH regulators of FSH secretion such as activin, inhibin or follistatin, used alone or in combination with abarelix, may allow us to more fully suppress this mitogenic pathway more effectively than the use of abarelix alone.

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