The Efficacy and Safety of Degarelix, a GnRH Antagonist: A 12-month, Multicentre, Randomized, Maintenance Dose-finding Phase II Study in Japanese Patients with Prostate Cancer

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Received December 28, 2011; accepted February 23, 2012

Objective: To assess the efficacy and safety of degarelix, a new gonadotropin-releasing hormone antagonist, for achieving and maintaining serum testosterone suppression (≤0.5 ng/ml) during the 12-month treatment of Japanese patients with prostate cancer.

Methods: This Phase II study was conducted as a multicentre, randomized, parallel-group, open-label study. A total of 273 patients with adenocarcinoma of the prostate (any stage) were treated. Degarelix was administered subcutaneously at an initial dose of 240 mg followed by monthly maintenance doses of either 80 or 160 mg for a total of 12 doses. The treatment continued for 12 months.

Results: Dose regimens of 240/80 and 240/160 mg maintained castrate levels of testosterone in 94.5 and 95.2% of the patients, respectively. After 3 days, 99.3 and 98.5% of the patients, respectively, reached these levels without a testosterone surge. Prostate-specific antigen levels decreased rapidly following degarelix administration and remained low throughout the study. Best overall response rates according to RECIST were 71.4 (20/28) and 72.7% (16/22), respectively. Eighteen patients (6.6%) withdrew from the study due to adverse events. The most common adverse events were injection site reactions; other adverse events included hot flush, nasopharyngitis, weight increase and pyrexia.

Conclusions: Both monthly degarelix dosing regimens were found to be effective in testosterone suppression without a testosterone surge, prostate-specific antigen reductions and anti-tumour effect in Japanese patients with prostate cancer, as was shown in the overseas Phase III study. Degarelix was also well tolerated.

Key words: Japan – clinical trial, Phase II – prostate cancer – gonadotropin-releasing hormone antagonist – androgen depletion therapy
INTRODUCTION

Prostate cancer is one of the most common types of cancer in men, and the mortality and morbidity due to prostate cancer are both increasing, especially in Asian countries. In Japan, the estimated number of prostate cancer patients was 42,997 in 2005. This number accounts for ~11% of all male cancer patients in Japan (estimated at 390,835) and is ranked third after gastric cancer and lung cancer (1).

As prostate cancer is sensitive to testosterone, androgen deprivation to decrease serum testosterone levels through orchietomy or drugs, and also drugs that block androgen receptor binding are widely used in therapy. Androgen deprivation therapy (ADT) is a standard treatment option in prostate cancer and is effective in most prostate cancer patients. Standard drugs used in ADT are gonadotropin-releasing hormone (GnRH) agonists, considered the best alternative to orchietomy for prostate cancer (2–5). A GnRH agonist reduces testosterone production by the testes by inducing down-regulation of GnRH receptors in the anterior pituitary. However, this mechanism of action can also provoke a flare-up effect that is accompanied by a transient increase in testosterone levels (testosterone surge) in the early stages of treatment (6,7). This effect may cause serious symptoms such as worsening of bone pain, ureteral obstruction and spinal cord compression in patients with advanced and/or metastatic prostate cancer. To prevent such events, antiandrogens are often used; however, adverse drug reactions and added cost need to be considered (2,8,9).

GnRH receptor antagonists have been developed that immediately suppress the release of gonadotropins, and thus testosterone, by binding competitively to pituitary GnRH receptors without inducing a testosterone surge (10,11).

Degarelix, a newly discovered GnRH antagonist, is intended for use in ADT for prostate cancer. Degarelix can reduce testosterone production quickly without provoking a transient increase in testosterone levels (testosterone surge) (12,13). In the overseas Phase III study, monthly degarelix regimens of 240/80 and 240/160 mg were not inferior to leuprolide at maintaining low testosterone levels over a 1-year treatment period, achieving a more rapid reduction in testosterone and prostate-specific antigen (PSA) levels than leuprolide without inducing testosterone surges or microsurges (14). Degarelix represents an effective therapy for inducing and maintaining androgen deprivation in patients with prostate cancer and has a different mechanism of action from traditional GnRH agonists. Its immediate onset of action achieves a more rapid suppression of testosterone and PSA than leuprolide, eliminating the need for flare protection. Based on these findings, the monthly degarelix regimen of 240/80 mg has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

The present study in Japanese patients was conducted to evaluate the efficacy and safety of degarelix, to compare the 240/80 and 240/160 mg regimens and to compare findings with the results of the overseas Phase III study. To characterize the effects of degarelix, tumour response was assessed using the RECIST guidelines and the General Rule for Clinical and Pathological Studies on Prostate Cancer.

PATIENTS AND METHODS

Patients

Male patients 20 years of age or older at the time of obtaining consent, with histologically confirmed prostate cancer (adenocarcinoma) of all stages, for whom endocrine treatment (except neoadjuvant hormonal therapy) was indicated, were included in the study. The population included patients with an increasing PSA level after treatment with curative intent, i.e. those with biochemical failure and those with metastatic disease (hormone-sensitive). The patients had to have a serum testosterone level above 1.5 ng/ml at screening, an ECOG (Eastern Co-operative Oncology Group) performance status (PS) score of 0–2 and a PSA of ≥2 ng/ml. The previous or current hormonal management of prostate cancer was not allowed, except in patients who had undergone localized therapy with curative intent in which neoadjuvant or adjuvant hormonal therapy for ≤6 months was accepted (if discontinued 6 months before inclusion). Patients considered to be candidates for curative therapy were excluded. The patient’s participation was discontinued if he had inadequate testosterone suppression (defined as testosterone > 1.0 ng/ml at one measurement or > 0.5 ng/ml at two consecutivemeasurements, from 1 month onwards) and progressive disease became evident.

Study Design

This was a Phase II, 12-month, maintenance dose-finding study in Japanese patients with prostate cancer. It was conducted using a multicentre, randomized, parallel-group, open-label, comparative design.

Patients were randomized through central allocation at Bellsystem24, Inc. Randomization in the study used the minimization method, with age (<75 or ≥75), prior treatment for prostate cancer (present, absent), clinical stage (localized prostate cancer, locally advanced prostate cancer or metastatic prostate cancer) and serum PSA level (<60 ng/ml, ≥60 ng/ml) used as adjustment factors.

In all, 278 patients were randomized and received an initial dose of degarelix of 240 mg (given as two 3 ml injections, 40 mg/ml) and thereafter monthly (every 28 days) maintenance doses of either 80 mg (one 4 ml injection of 20 mg/ml; n = 136) or 160 mg (40 mg/ml; n = 137) for 12 months (Fig. 1). Degarelix was supplied as a freeze-dried powder for suspension in water. Injections were given subcutaneously in predefined areas of the abdomen.

All patients provided written consent to participate before any study-related activities commenced. The trial was conducted in accordance with the principles of the Declaration...
of Helsinki as well as Good Clinical Practice Guidelines (15). The Institutional Review Board at all participating institutions approved the protocol.

ASSESSMENTS

The primary endpoint was the proportion of patients with a serum testosterone level of ≤0.5 ng/ml between 28 and 364 days, which was considered a treatment response.

The main secondary endpoints included the proportion of patients with a serum testosterone level of ≤0.5 ng/ml at Day 3 of treatment, the proportion of patients with a testosterone surge during the first 14 days of treatment, time to the recurrence of serum PSA (defined as a PSA increase of 50% or more from the nadir and at least 5 ng/ml on two consecutive visits at least 2 weeks apart), pharmacodynamic parameters [serum testosterone, PSA, luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] over time, the overall response rate according to ‘Assessment Criteria of Response to Noninvasive Treatment for Prostate Cancer (General Rule for Clinical and Pathological Studies on Prostate Cancer [the 3rd Edition])’ and tumour response rate (overall response rate) using the RECIST guidelines by an external neutral review board (16,17). Assessment Criteria of Response to Noninvasive Treatment for Prostate Cancer defined by the Japanese Urological Association are a modification of World Health Organization (WHO) criteria (18), which include assessment of subordinate variables such as a primary focus, PSA, a metastatic lesion etc. Serum testosterone, serum PSA, serum LH and serum FSH levels were measured by SRL Inc. in accordance with Good Laboratory Practice. A central laboratory (SRL) performed serum testosterone measurements in accordance with Good Laboratory Practice, using a validated method for low-range detection of testosterone levels.

Safety assessments included laboratory values (biochemistry, haematology and urinalysis), adverse events (AEs), vital signs and 12-lead electrocardiograms. AEs were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0.

STATISTICAL ANALYSIS

The primary analysis population was the full analysis set (FAS), defined as patients who received the study drug and in whom at least one efficacy variable (either the primary or secondary variables) was evaluated after administration, and Completers-FAS (C-FAS), which was defined as FAS patients who completed the study or who showed a serum testosterone level exceeding 0.5 ng/ml after Visit 7 (Day 28 of treatment). The primary efficacy endpoint was the proportion of patients with serum testosterone suppression ≤0.5 ng/ml from Days 28 through 364. The primary analysis was performed to obtain the proportion of patients; the 95% confidence interval (CI) was calculated by the Clopper–Pearson method (C-FAS). A secondary analysis was the cumulative probability estimated by the Kaplan–Meier method (FAS). Secondary efficacy endpoints were the testosterone surge during the first 14 days (FAS), the serum testosterone level ≤0.5 ng/ml at Day 3 (FAS), PSA failure from Days 0 through 364 (FAS), best overall response rate according to the RECIST guidelines (FAS) and overall response rate based on Assessment Criteria of Response to Noninvasive Treatment for Prostate Cancer (FAS). The proportion of patients who met each endpoint criteria was calculated; the 95% CIs were calculated by the Clopper–Pearson method.

RESULTS

PATIENT DEMOGRAPHICS AND DISPOSITION

A total of 358 patients were screened, 278 patients were randomized and 273 patients received study medication,
comprising the FAS/safety analysis set (Fig. 2). Of the entire study population, four patients violated at least one predefined criterion, constituting a major protocol deviation, and were therefore excluded from the per-protocol analysis set.

There were 208 (76.2%) patients who completed the 12-month study. Eighteen patients (6.6%) withdrew due to AEs, 44 (16.1%) due to lack of efficacy, including inadequate testosterone suppression according to the pre-specified withdrawal criteria, and 3 (1.1%) due to other reasons including withdrawal of consent.

There were few differences between the two treatment groups with respect to demographics and baseline characteristics (Table 1).

**EFFICACY**

**TESTOSTERONE LEVELS**

The proportion of patients with serum testosterone suppression \( \leq 0.5 \text{ ng/ml} \) from Days 28 through 364 (primary endpoint) was 94.5% \( (n = 104, 95 \text{ CI}: 88.5–98.0\%) \) in the 240/80 mg group and 95.2% \( (n = 100, 95 \text{ CI}: 89.2–98.4\%) \) in the 240/160 mg group (Table 2). The cumulative probability was 94.9% \( (n = 130, 95 \text{ CI}: 90.9–98.9\%) \) in the 240/80 mg group and 95.7% \( (n = 132, 95 \text{ CI}: 92.1–99.4\%) \) in the 240/160 mg group, showing that the lower limit of the 95 CI exceeded 90% in both groups. Thus, the study fulfilled the FDA criteria for efficacy.

From Days 0 to 28, treatment with degarelix resulted in a rapid suppression of testosterone levels; by Day 3, the median testosterone levels were \( \leq 0.5 \text{ ng/ml} \) in 99.3 and 98.5% of the patients in the degarelix 240/80 and 240/160 mg groups respectively, without a testosterone surge (Table 3). In addition, testosterone levels were measured to assess the GnRH agonist stimulation (microsurge) on Days 255 and 259 after the ninth maintenance dose (Day 252). In both groups, the mean testosterone levels at Days 255 and/or 259 slightly decreased from those at Day 252. Serum testosterone was maintained at low levels throughout the study (Fig. 3A).

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**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Degarelix 240/80 mg (n = 136)</th>
<th>Degarelix 240/160 mg (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>74.7 (6.76)</td>
<td>74.2 (7.19)</td>
</tr>
<tr>
<td>Median testosterone, ng/ml (1Q–3Q)</td>
<td>4.52 (3.74–5.71)</td>
<td>4.31 (3.47–5.35)</td>
</tr>
<tr>
<td>Median PSA, ng/ml (1Q–3Q)</td>
<td>24.65 (9.90–92.60)</td>
<td>20.20 (6.92–69.60)</td>
</tr>
<tr>
<td>Stage of disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized (^a)</td>
<td>61 (44.9)</td>
<td>64 (46.7)</td>
</tr>
<tr>
<td>Locally advanced (^b)</td>
<td>42 (30.9)</td>
<td>41 (29.9)</td>
</tr>
<tr>
<td>Metastatic (^c)</td>
<td>33 (24.3)</td>
<td>31 (22.6)</td>
</tr>
<tr>
<td>Not classifiable</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Gleason score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>5–6</td>
<td>19 (14.0)</td>
<td>22 (16.1)</td>
</tr>
<tr>
<td>7–10</td>
<td>117 (86.0)</td>
<td>114 (83.2)</td>
</tr>
</tbody>
</table>

\(^a\)Localized = T1/2, NX or N0, and M0.  
\(^b\)Locally advanced = T3/4, NX or N0, and M0, or N1 and M0.  
\(^c\)Metastatic = M1.

**Table 2. Proportion of patients with testosterone \( \leq 0.5 \text{ ng/ml} \) from Days 28 through 364, C-FAS**

<table>
<thead>
<tr>
<th></th>
<th>Degarelix 240/80 mg (n = 110)</th>
<th>Degarelix 240/160 mg (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone ( \leq 0.5 \text{ ng/ml} ), n (%)</td>
<td>104 (94.5) (88.5, 98.0)</td>
<td>100 (95.2) (89.2, 98.4)</td>
</tr>
<tr>
<td>Testosterone ( &gt;0.5 \text{ ng/ml} )</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

C-FAS, Completers-full analysis set.
PROSTATE-SPECIFIC ANTIGEN

Serum PSA levels decreased rapidly following degarelix administration. The median rate of change in PSA levels up to Day 14 was $-62.48\%$ in the 240/80 mg group and $-62.02\%$ in the 240/160 mg group. At Day 28, this rate was, respectively, $-80.14$ and $-79.52\%$, showing a rapid decrease in PSA levels in both groups. Serum PSA was maintained at low levels throughout the study in both groups (Fig. 3B).

LUTEINIZING HORMONE/FOLLICLE-STIMULATING HORMONE

After administration of degarelix, the median LH and FSH levels decreased rapidly and remained suppressed until the end of the study. The median reduction in LH at Day 1 compared with baseline was $85\%$ with 240/80 mg and $84.15\%$ with 240/160 mg, and $93.96$ and $93.95\%$, respectively, at the end of the study. At the end of the study, the median reduction in FSH compared with baseline was $83.55$ and $81.83\%$ with each dosing regimen.

ANTI-TUMOUR EFFECT

The best overall response according to the RECIST guidelines [complete response (CR) + partial response (PR)] was $71.4\%$ in the 240/80 mg group and $72.7\%$ in the 240/160 mg group, revealing a good anti-tumour effect (Table 4).

The overall response rate based on Assessment Criteria of Response to Noninvasive Treatment for Prostate Cancer was defined as the sum of CRs and PRs. The overall response rate (CR + PR) in the 240/80 and 240/160 mg groups was, respectively, $77.4$ and $80.9\%$ on Day 28, $90.8$ and $90.5\%$ on Day 84 and $84.5$ and $87.1\%$ on Day 364, showing a rapid and sustained anti-tumour effect.

SAFETY

Treatment-emergent AEs were reported for a comparable percentage of patients in both groups: $94.1\%$ of the patients in the 240/80 mg group and $94.9\%$ in the 240/160 mg group (Table 5).

The most common AEs were injection site reactions, which occurred in $48.0\%$ of pooled degarelix patients. Other AEs included hot flush ($27.8\%$), nasopharyngitis ($27.1\%$), weight increase ($15.8\%$) and pyrexia ($13.6\%$).

Injection site reactions such as pain, erythema and induration were frequently observed, but were mostly Grade 1 or 2. Grade 3 injection site pain was noted in one patient only and did not lead to the patient's withdrawal. The number of patients who discontinued treatment due to injection site reactions was three (2.2\%) and all of these were in the 240/160 mg group. There were no serious injection site reactions or injection site reactions leading to death.

Table 3. Proportion of patients with a testosterone surge during the first 14 days of treatment, FAS

<table>
<thead>
<tr>
<th></th>
<th>Degarelix 240/80 mg (n = 136)</th>
<th>Degarelix 240/160 mg (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone surge, n (%) (95% CI)</td>
<td>0 (0.0, 2.7)</td>
<td>0 (0.0, 2.7)</td>
</tr>
</tbody>
</table>

Testosterone surge: increases of at least 15% in the serum testosterone level from baseline (Day 0 of treatment) were found on at least two measurement days within 14 days of administration.

Table 4. Best overall response rate according to the RECIST guidelines, FAS

<table>
<thead>
<tr>
<th></th>
<th>Degarelix 240/80 mg (n = 28)</th>
<th>Degarelix 240/160 mg (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response rate, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (complete response)</td>
<td>1 (3.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR (partial response)</td>
<td>19 (67.9)</td>
<td>16 (72.7)</td>
</tr>
<tr>
<td>SD (stable disease)</td>
<td>8 (28.6)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>PD (progressive disease)</td>
<td>0 (0)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>NE (not evaluated)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CR + PR</td>
<td>20 (71.4)</td>
<td>16 (72.7)</td>
</tr>
</tbody>
</table>
Frequently observed AEs other than injection site reactions were hot flush and weight increase, and these were associated with the pharmacological effect of ADT. These events were mostly mild or moderate in severity.

Overall, 16 (11.8%) patients in the 240/80 mg group reported serious AEs, compared with 17 (12.4%) patients in the 240/160 mg group.

Deaths occurred in two patients: one in the 240/80 mg group and one in the 240/160 mg group. One patient in the 240/80 mg group was 78 years old, who developed diffuse large B-cell lymphoma and abnormal hepatic function 21 days after the ninth maintenance dose. Cerebral haemorrhage occurred the following day, and the patient died of cerebral haemorrhage 4 days later. All the AEs were determined to be ‘possibly related’ to the study drug. Another 84-year-old patient in the 240/160 mg group developed interstitial lung disease 6 days after the ninth maintenance dose. Sepsis occurred 25 days later, and the patient died of sepsis 3 days thereafter. The sepsis and interstitial lung disease were determined to be ‘not related’ and ‘possibly related’, respectively, to the study drug.

Seven patients (5.1%) in the 240/80 mg group and 11 patients (8.0%) in the 240/160 mg group withdrew from the study due to AEs.

In the 240/80 mg group, there were no AEs that occurred in two or more patients and led to treatment discontinuation, whereas such AEs were reported in the 240/160 mg group, which included injection site induration (three patients), malaise (two patients) and abnormal hepatic function (two patients).

There were no clinically significant changes in clinical laboratory values and vital signs. The AEs observed were mostly similar between the treatment groups.

### DISCUSSION

The primary objective of this study was to investigate whether degarelix suppressed serum testosterone, an established surrogate endpoint for prostate cancer, to castrate levels (<0.5 ng/ml) (3). In each treatment group, the lower limit of the 95% CI of the cumulative castration rate exceeded 90%. This result closely coincided with the results of the overseas Phase III study, demonstrating the similarity between the findings of the two studies (14).

The overall response rates determined using the Assessment Criteria of Response to Noninvasive Treatment for Prostate Cancer were 90.8 and 90.5% on Day 84, and 84.5 and 87.1% on Day 364 in the 240/80 and 240/160 mg groups, respectively, showing a sustained anti-tumour effect. The rates on Day 84 were not markedly different from the tumour response rates previously reported for GnRH agonists (19,20). The overall response rate had already reached ≏80% on Day 28. This rapid anti-tumour effect also demonstrated the ability of degarelix to achieve and maintain testosterone suppression quickly, without inducing a testosterone surge.

With regard to safety, the long-term (1 year) tolerability of degarelix in Japanese patients with prostate cancer was confirmed in the 240/80 and 240/160 mg groups. Though hot

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Degarelix 240/80 mg (n = 136)</th>
<th>Degarelix 240/160 mg (n = 137)</th>
<th>Degarelix total (n = 273)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grades 3–5</td>
<td>All grades</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>All adverse events</td>
<td>128</td>
<td>94.1</td>
<td>21</td>
</tr>
<tr>
<td>Any injection site reaction</td>
<td>63</td>
<td>46.3</td>
<td>—</td>
</tr>
<tr>
<td>Hot flush</td>
<td>45</td>
<td>33.1</td>
<td>—</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>33</td>
<td>24.3</td>
<td>—</td>
</tr>
<tr>
<td>Weight increase</td>
<td>25</td>
<td>18.4</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18</td>
<td>13.2</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>7.4</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>2.9</td>
<td>—</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7</td>
<td>5.1</td>
<td>—</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>4</td>
<td>2.9</td>
<td>—</td>
</tr>
<tr>
<td>Malaise</td>
<td>5</td>
<td>3.7</td>
<td>—</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>2.2</td>
<td>—</td>
</tr>
<tr>
<td>Contusion</td>
<td>1</td>
<td>0.7</td>
<td>—</td>
</tr>
</tbody>
</table>
flush and weight increase were observed as AEs associated with decreased testosterone levels, mainly due to ADT, all were tolerable.

While injection site reactions were frequently noted, they were almost all mild or moderate in severity with little clinical significance, allowing most of the affected patients to continue receiving study treatment. Compared with the overseas Phase III study, the incidence of injection site reactions was slightly higher in this study (14). However, the intensity of injection site reactions was not much different between the two studies. Injection site reactions were also reported with GnRH agonist administrations. In the overseas Phase III study that compared degarelix with leuprolide, degarelix had a higher rate of injection site reactions than did leuprolide [intramuscular (i.m.)]. This difference in injection site reactions might be due to the different route of administration (subcutaneous vs. i.m.) and the injection volume.

There were no marked differences in safety between the 240/80 and 240/160 mg groups. The types and incidence of AEs observed in this study were not substantially different from those reported in previous clinical studies of ADTs. Though the incidence of AEs was higher in this study than in the overseas Phase III study, there was no marked difference between the two studies in terms of the type and occurrence of serious AEs and AEs leading to treatment discontinuation.

It is known that the concomitant use of any antiandrogen at the start of GnRH agonist treatment can reduce the incidence of serious exacerbation of symptoms (flare-up), such as worsening of bone pain, ureteral obstruction and spinal cord compression, in patients with advanced and/or metastatic prostate cancer, though not completely (9). This study demonstrated that degarelix suppressed serum testosterone in most patients (>98%) on Day 3 and in all patients on Day 28 to castrate levels (<0.5 ng/ml) without inducing a testosterone surge in the early stage of treatment with a GnRH agonist, which can cause flare-up of symptoms. A rapid onset of suppression of testosterone production was thus confirmed for degarelix. This finding indicates that it is unnecessary to use an antiandrogen to prevent flare-ups when administering treatment with degarelix (21).

These characteristics were also demonstrated in the overseas Phase III study, which showed that degarelix reduced PSA levels more quickly than leuprolide (14). The Phase III study also reported that patients with prostate cancer at any stage who were treated with degarelix at 240/80 mg, the dose approved overseas, had a higher likelihood of 1-year survival without an increase in PSA levels, in comparison with those who were treated with leuprolide. The same study also showed that PSA relapse-free survival was prolonged by degarelix in patients with high baseline PSA levels (PSA > 20 ng/ml) (22,23). Furthermore, an extension of this Phase III study reported that PSA progression-free survival was significantly improved by switching from leuprolide to degarelix (24).

In Japan, it has been common practice to provide endocrine treatment not only to patients with metastatic prostate cancer but also to patients with localized or locally advanced prostate cancer. The treatment was chosen for ~57% of the patients with Stage T1–T4 disease and ~46% of those with Stage T1–T3 disease (25). Combined androgen blockade (CAB) with the concomitant use of an antiandrogen has also been provided to more than 60% of low- to high-risk cancer patients (26). The results of the Phase III study demonstrated that combination treatment with leuprolide and bicalutamide and monotherapy with degarelix had a similar effect on PSA levels during 1-month administration (22). Therefore, CAB with degarelix and an antiandrogen agent is expected to have a more rapid and pronounced effect than that obtainable with conventional CAB with a GnRH agonist. Further investigation will be conducted in the future.

CONCLUSION

In this Japanese Phase II study of degarelix in Japanese patients with prostate cancer, the results in the 240/80 and 240/160 mg groups were almost equivalent in terms of efficacy and similar to the results of the overseas Phase III study. No marked difference was detected in the safety profiles of these two groups, suggesting that there was little difference related to dosing. This finding is similar to that in the Phase III study.

Taking the risk–benefit balance for efficacy and safety into consideration, an appropriate monthly degarelix dosing regimen for Japanese patients with prostate cancer is an initial dose of 240 mg followed by a maintenance dose of 80 mg. This is identical to the clinical dosage approved overseas.

Acknowledgements

We would like to express our gratitude to the investigators at the following participating institutions. Participating institutions (Japan): Hokkaido Memorial Hospital of Urology, Sapporo Medical University Hospital, Hirosaki University School of Medicine and Hospital, Iwate Medical University Hospital, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, Gunma University Hospital, Tsukuba University Hospital, Chiba University Hospital, Chiba Cancer Center, Kameda Clinic, The University of Tokyo Hospital, Nihon University Itabashi Hospital, Kyorin University Hospital, Mitsui Memorial Hospital, Tokyo Metropolitan Fuchu Hospital, Teikyo University Hospital, Tokyo Medical University Hospital, Tokyo Medical and Dental University—University Hospital of Medicine, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Jikei University Hospital, Keio University Hospital, Yokohama City University Hospital, Kitasato University Hospital, Yokohama Minami Kyousai Hospital,
Yokohama City University Medical Center, Yokohama Municipal Citizen’s Hospital, Yokosuka Kyoai Hospital, Niigata University Medical and Dental Hospital, Niigata Cancer Center Hospital, Nagano Municipal Hospital, Shinonoi General Hospital, Kanazawa University Hospital, Hamamatsu University School of Medicine University Hospital, Seirei Mikatahara General Hospital, Kyoto University Hospital, University Hospital Kyoto Prefectural University of Medicine, Osaka University Hospital, Osaka City University Hospital, Osaka City General Hospital, Kinki University School of Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Sumitomo Hospital, Kobe University Hospital, Nishi-Kobe Medical Center, Kobe City Medical Center General Hospital, Tenri Hospital, Nara Medical University Hospital, Japanese Red Cross Society Wakayama Medical Center, Okayama University Hospital, Kurashiki Central Hospital, Japanese Red Cross Okayama Hospital, Hiroshima University Hospital, Yamaguchi University Hospital, Yamaguchi-ken Saiseikai Shimonoseki General Hospital, Tokushima University Hospital, Kagawa University Faculty of Medicine, Kyusyu University Hospital, Harasanshin Hospital, Kurume University Hospital, Kumamoto Chuo Hospital, Nagasaki University Hospital and Kagoshima University Medical and Dental Hospital

Funding
This work was supported by Astellas Pharma Inc.

Conflict of interest statement
Hideki Maeda, Yuji Fukuyama and Kentarō Takeda are employees of Astellas Pharma Inc. Yasuo Ohashi reports receiving a consultation fee from Astellas Pharma Inc. Hideyuki Akaza, Seichiro Ozono, Taji Tsukamoto and Seiji Naito are paid by Astellas Pharma Inc. for medical advice on degarelix.

References