# Comparison of efficacy and safety of one- and three-month luteinizing hormone-releasing hormone agonist depots as initial therapies for prostate cancer

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**Abstract**

**Background:** We compared the efficacy and safety in prostate cancer patients of 1- and 3-month depots of the luteinizing hormone-releasing hormone (LH-RH) agonist goserelin acetate.

**Patients and Methods**: Patients were randomly assigned to the Direct Group that received the goserelin 3-month depot or the Switch Group that began with the 1-month depot for the first 3 months and then switched to the 3-month depot. All patients were co-administered the anti-androgen agent bicalutamide. Serum testosterone and prostate-specific antigen (PSA) levels and adverse events were recorded at Weeks 4, 8, 12, and 24.

**Results**: Baseline testosterone levels in the Direct and Switch Groups were 4.98 ng/mL and 5.07 ng/mL respectively (P=0.798). At each week, the levels of both groups were ≤0.50 ng/mL (castration level) with no significant differences between them. All of the patients of the Switch Group and 98.1% of the Direct Group achieved castration levels at Week 12, and 100% achieved it at Week 24. Baseline PSA levels in the Direct and Switch Groups were 52.37 and 46.72 ng/mL respectively (P=0.793). Levels in both groups dropped continuously to about 1.0 ng/mL at Week 24 with no significant differences between them at any time. Three patients of the Direct Group experienced adverse events that were attributed to the co-administered

bicalutamide.

**Conclusions**:There was no difference in the efficacy or safety between the 1-month and 3-month depots of goserelin when given as initial prostate cancer treatment in combination with bicalutamide. Patients must be monitored for adverse events associated with bicalutamide. (249/250)

**Mini-abstract**

Initial administration of goserelin 3-month depot as androgen deprivation therapy in prostate cancer patients has no major efficacy or safety issues.

**Keywords**

Prostate cancer, androgen deprivation therapy, luteinizing hormone-releasing hormone agonist

## Introduction

Ever since Huggins and Hodges reported the hormone dependency of prostate cancer in 1941,[1] androgen deprivation therapy (ADT) has been the standard medical therapy. Initially surgical castration or estrogen therapy was used as ADT. However, with the introduction of luteinizing hormone-releasing hormone (LH-RH) agonists, medical castration has become widely used around the world.

Two such agonists, goserelin acetate and leuprorelin acetate, are now approved for clinical use in Japan, and 1-month and 3-month depots are currently available. Advantages of the 3-month depot include reductions of (1) hospital visits by one-third, (2) physical and/or psychological burden with the injections, (3) and drug costs. Because of these benefits, use of the 3-month depot from the start of treatment is ideal. However, while reports are available on the efficacy and safety of the 3-month depot administered as the initial treatment in Western patients,[2,3] there is only one report, based on a very small population, that evaluated the efficacy and safety in Japanese patients.[4] Because of this minimal substantiation, many Japanese physicians start treatment with the 1-month depot and then switch to the 3-month depot after confirming its efficacy and safety. Therefore we performed a clinical study to compare the efficacy and safety of the LH-RH agonist goserelin acetate in patients who

received the 3-month depot from the start of treatment with those who initially received the 1-month depot for the first three months and then switched to the 3-month depot.

## Patients and Methods

This was a multicenter, randomized controlled study with an open-label, parallel group design and was approved by the institutional review board at the Shinshu University Hospital and at each of the other participating hospitals (see Appendix 1). All patients provided written informed consent. Between June 1, 2007 and December 31, 2010, 120 patients were recruited from Shinshu University Hospital (Nagano, Japan) and hospitals in its neighborhood. The study included patients with 2002 Union for International Cancer Control[5] clinical stage T3-4, NX, and MX advanced prostate cancer or T1-2, N0, or M0 prostate cancer for whom definitive therapy was not indicated. Eligible patients needed to have an Eastern Cooperative Oncology Group performance status[6] of 0 or 1, white blood cell count of at least 3000/$mm^3$, hemoglobin of more than 10.0 g/dl, platelet count of more than $7.5x10^4/mm^3$, aspartate aminotransferase (AST) of less than 2.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) of less than 2.5 x ULN, alkaline phosphatase (ALP) of less than 2.5 x ULN, and creatinine of less than 1.5 x ULN at study entry. Patients with a history of hormonal therapy (surgical and medical castration), chemotherapy, operative therapy, or radiation therapy were excluded. Patients meeting any of the following criteria were withdrawn from the study: (1) disease progression, (2) any adverse event that in the opinion of the physicians justified the discontinuation of

treatment, (3) toxicity of grade 4,[7] or (4) withdrawal of consent for participation by the patient.

The patients were randomly assigned to the Switch Group (n = 60) or the Direct Group (n = 60). Patients in the Switch Group were initially treated with monthly with injections of the 1-month depot of goserelin acetate (Zoladex® 3.6 mg depot, AstraZeneca, Osaka, Japan) for three months. They were then switched to 3-month depot (Zoladex LA® 10.8 mg depot). In the Direct Group, the 3-month depot of goserelin acetate (Zoladex LA® 10.8 mg depot) was administrated at the start of the treatment and then again three months later. In Japan, to ensure complete androgen blockade, treatment with an LH-RH agonist is often accompanied by an anti-androgen agent. This combined androgen blockade (CAB) also reduces the possibility of a flare-up associated with the LH-RH agonist alone. Therefore we supplemented the goserelin acetate with the orally administered anti-androgen agent bicalutamide (Casodex® 80 mg, AstraZeneca) once daily during the treatment period.

*Clinical data*

Patient backgrounds, including clinical stage, Gleason score,[8] and prostate-specific antigen (PSA) level at diagnosis, were collected at the time of registration. Blood samples were taken in the morning before the administration of the LH-RH agonist, as well as at Weeks 4, 8,

12, and 24. Total testosterone was measured by radioimmunoassay (Mitsubishi Chemical Medience Co., Tokyo, Japan). Other laboratory data, including PSA, were measured at each hospital.

*Endpoints and statistical analysis*

The primary endpoint was the suppression of serum testosterone at Weeks 4, 8, 12, and 24. Student's t-test was used to compare the testosterone levels between the two groups. Successful castration was defined as achieving a serum testosterone of ≤0.50 ng/mL, and the proportion of patients in each group achieving that level of suppression was determined. Secondary endpoints were the mean values of PSA and normalization rates, defined as the proportion of patients with PSA levels less than 4.0 ng/mL at Weeks 4, 8, 12, and 24.

Adverse events were evaluated during the entire treatment period by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, ver. 3.0).[9] All Grade 1 or above adverse events, including laboratory test abnormalities, were summarized. Chi-square test or Fisher's exact test was used to compare the proportion of adverse events between the groups. Adverse incidences were summarized for four periods: Weeks 0-4, Weeks 5-8, Weeks 9-12, and Weeks 13-24.

All statistical tests were two-sided, and the data were analyzed using SPSS® version

18.0 (SPSS, Chicago, IL, USA).

## Results

After the randomized distribution into the two study groups, four patients in the Switch Group dropped out by withdrawing consent. Also, 15 patients (9 in the Switch Group and 6 in the Direct Group) were excluded from the analysis because through error, they received only a small portion of the protocol treatment or some test data was not measured. Thus, 47 patients in the Switch Group and 54 patients in the Direct Group were included in the analysis.

### *Patient characteristic*

The mean age in the Switch Group was 76.3 years old, which was slightly, but not significantly, higher than 75.0 in the Direct Group (Table 1). While the Gleason score and performance status were slightly higher in the Direct Group, there were no significant differences between the two groups (P=0.290 and P=0.282, respectively). Other factors, including testosterone and PSA levels and clinical stages, were also well balanced between the two groups.

### *Testosterone suppression*

At the initial diagnosis, the testosterone level in the Switch Group and the Direct Group were 4.98 ng/mL and 5.07 ng/mL, respectively (P=0.798, Table 1). At Week 4, the levels for both groups (Fig. 1) had dropped significantly to 0.13 ng/mL (P<0.001) and 0.17 ng/mL

(P<0.001) in the Switch Group and the Direct Group respectively. There was no significant difference between the two groups (P=0.189). After Week 8, the testosterone levels remained less than or equal to 0.20 ng/mL in both groups, with no significant difference between them (Fig. 1). While most of the patients were maintained at the castrate level of ≤0.50 ng/mL after Week 4 (Table 2), a temporary escape from the castrate range occurred in two patients of the Direct Group. In one case the patient's testosterone level at baseline was 4.88 ng/mL, and it decreased to only 1.35 ng/mL four weeks after the administration of goserelin 3-month depot. However, at Weeks 8 and 12, the levels were suppressed below the castrate range. In the other case, the patient's testosterone level at baseline was 6.00 ng/mL and was suppressed to 0.30 ng/mL and 0.07 ng/mL at Weeks 4 and 8, respectively. However, it increased to 0.77 ng/mL at Week 12, but then decreased again to 0.27 ng/mL at Week 24.

*Prostate-specific antigen*

The mean PSA levels in the Switch and Direct Groups at Weeks 4 dropped to 8.99 ng/mL and 8.53 ng/mL from baseline, respectively (Table 3). They continued to gradually decrease, reaching 1.01 ng/mL and 0.91 ng/mL at Week 24, respectively. There were no significant differences between the groups in the PSA levels at any point. The percent of patients with PSAs of less than 4.0 ng/mL at Week 12 were 93.5% (43/46) in the Switch Group

and 95.8% (46/48) in the Direct Group. At Week 24, the percents were 95.0% (38/40) and 95.8% (46/48), respectively. There were no significant differences between the groups.

*Adverse events*

There were more adverse events in the period of Weeks 0-4. During that time, the occurrence of adverse events in the Switch Group, 53.2% (25/47), was slightly lower than in the Direct Group, 57.4% (31/54), but the difference was not significant (P=0.671). During the period of Weeks 5-8, there were more occurrences in the Switch Group, 19.1% (9/47), compared to the Direct Group, 9.3% (5/54), but the difference was not significant (P=0.151). While the cumulative incidence through Week 8 was 72.3% (34/47) in the Switch Group, slightly higher than the 66.7% (36/54) in the Direct Group, the difference was not significant (P=0.538). After Week 9, the number of adverse events gradually decreased, and the incidences throughout the whole study period were comparable in the two groups at 88.1% (37/42) in the Switch Group and 82.4% (42/51) in the Direct Group (Fig. 2).

On the advice of the attending physicians, three patients in the Direct Group were withdrawn due to adverse events (Table 4). The first patient had an onset of peripheral edema of Grade 1 in the period of Week 0-4, but the symptoms disappeared after discontinuation of bicalutamide. For the second patient, AST and ALT increases of Grade 3 occurred at Week 8.

Again, these values became normalized after one month following discontinuation of bicalutamide. In the third patient, AST, ALT, and ALP levels were slightly elevated at Week 4 with increases of Grade 1. The discontinuation of bicalutamide resulted in normalization of those values in the following month. No patient from the Switch Group was withdrawn from protocol treatment due to any adverse event.

## Discussion

While there were no differences in testosterone levels between the two groups in this study, escape from the castrate level of 0.5 ng/mL occurred in two patients in the Direct Group. For these two patients, there was no sign of flare-up, and PSA levels decreased over time. There are several other studies that describe cases of testosterone escape during treatment with LH-RH agonists. Oefelein et al. reported in their prospective study that escape from the castrate level occurred in approximately 5% of patients with prostate cancer who were receiving the 3-month depot of leuprorelin acetate or goserelin acetate.[10] In their retrospective series, Yri et al. reported an escape rate of 10% for patients receiving leuprorelin acetate 3-month depot.[11] Meanwhile, some reports indicate that more than 10% of patients do not reach the castrate levels of testosterone with surgical castration (orchidectomy).[12, 13] These unexpected findings could be the result of individual differences in adrenal androgen concentration.[13] As the escape from the castrate level observed in this study was transient, and PSA was stably maintained at low levels, we believe that the efficacy of the 3-month goserelin acetate depot from the beginning of treatment is comparable to the treatment started with the 1-month depot.

Japanese and other studies have shown that there are no differences in adverse events

and safety profiles between the 1-month and 3-month depots when goserelin acetate is used alone.[2-4] In the study reported here, the anti-androgen bicalutamide was used in conjunction with the goserelin acetate. We found no difference in the incidence of adverse events between two groups, and thus we consider that the safety of treatment initiated with the 3-month depot is comparable to that of treatment initiated with the 1-month depot. In this study, three patients in the Direct Group had adverse events leading treatment discontinuation. One patient had peripheral edema and two had abnormalities in liver enzymes; however all of them recovered after the bicalutamide was discontinued. Therefore, these are considered to be the adverse events associated with bicalutamide. Liver damage and failure are known adverse reactions to bicalutamide,[14] and therefore hepatic function must be monitored regularly. Accordingly, regardless of the formulation of LH-RH agonist, we consider that patients who are on the CAB therapy should be monitored monthly for adverse events right after treatment is initiated. For patients using the 3-month depot, the benefit of reduced frequency of hospital visits will be lost. However, the other advantages, such as alleviated pain by reduced number of administrations and reduced drug cost, still remain.

In summary, this study showed that the efficacy and safety of the 3-month depot of goserelin acetate are comparable with that of the 1-month depot.

## Conflict of interest

The authors declare that there are no conflicts of interest.

Appendix 1

| Affiliation | Name |
|---|---|
| Shinshu University Hospital | Osamu Nishizawa |
| | Osamu Ishizuka |
| | Masako Kawakami |
| | Yoshiki Kurizaki |
| | Hiroo Inoue |
| | Tomoaki Tanabe |
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| | Masakuni Ishikawa |
| | Takayuki Kamigaito |
| Nagano Municipal Hospital | Syuji Nishizawa |
| | Manabu Ueno |
| | Ryo Nakatoh |
| Satoh Continence Clinic | Tomoya Satoh |
| Shinonoi General Hospital | Masahisa Wajiki |
| Japanese Red Cross Suwa Hospital | Hideo Kiyokawa |

| | |
|---|---|
| Omachi Municipal General Hospital | Yoshihiro Inoue |
| Komoro Kosei General Hospital | Shinya Kobayashi |
| Shinshu Ueda Medical Center | Hiroya Mizusawa |
| Nagano Matsushiro General Hospital | Tatsuo Nakagawa |
| Aizawa Hospital | Kenji Yamaguchi |
| Furuhata Urology Clinic | Masayuki Furuhata |
| Hokushin General Hospital | Hideki Mizuno |
| Matsumoto Medical Center | Itsuki Komiyama |

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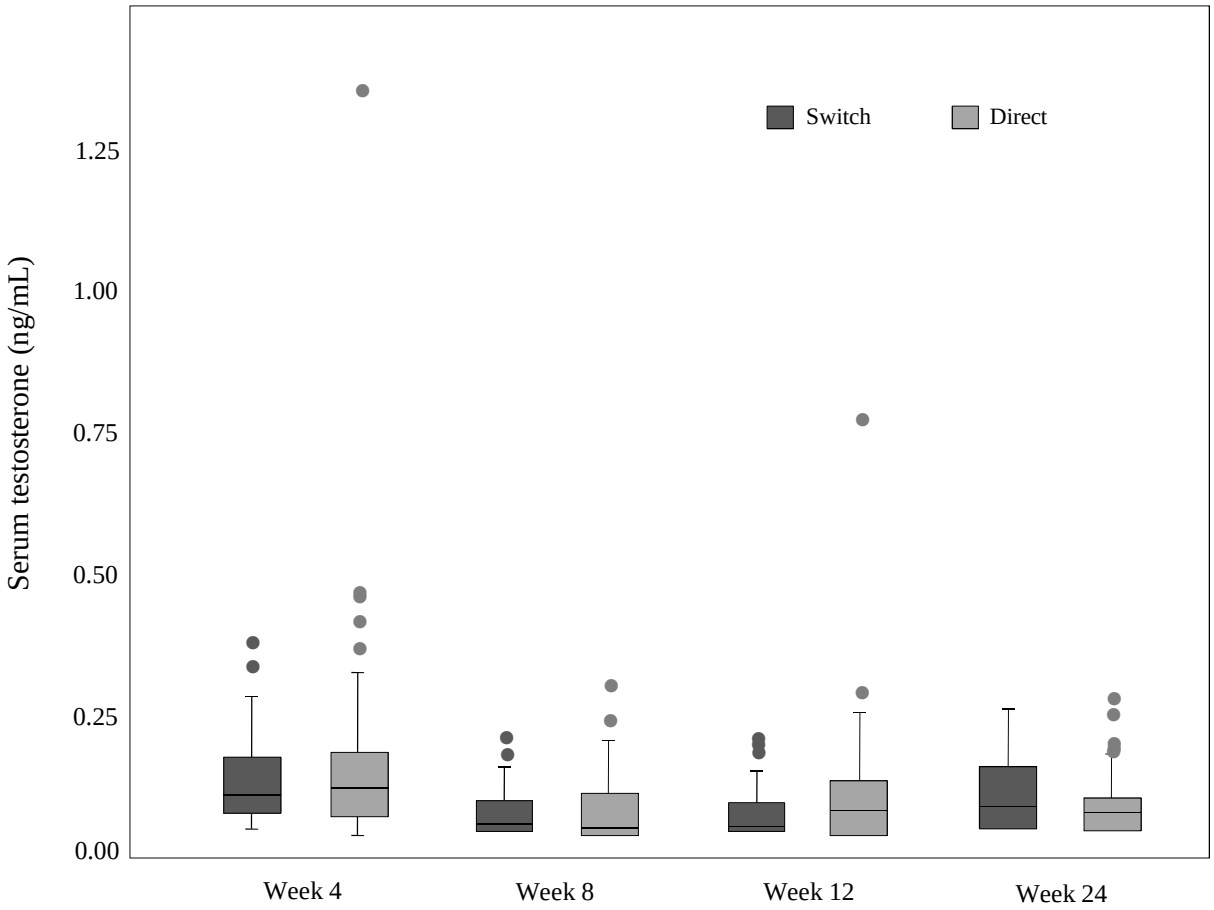
14) http://www.drugs.com/pro/casodex.html

**Legends to Figures**

Fig. 1. Serum testosterone levels.

Fig. 2. Occurrence of adverse events.

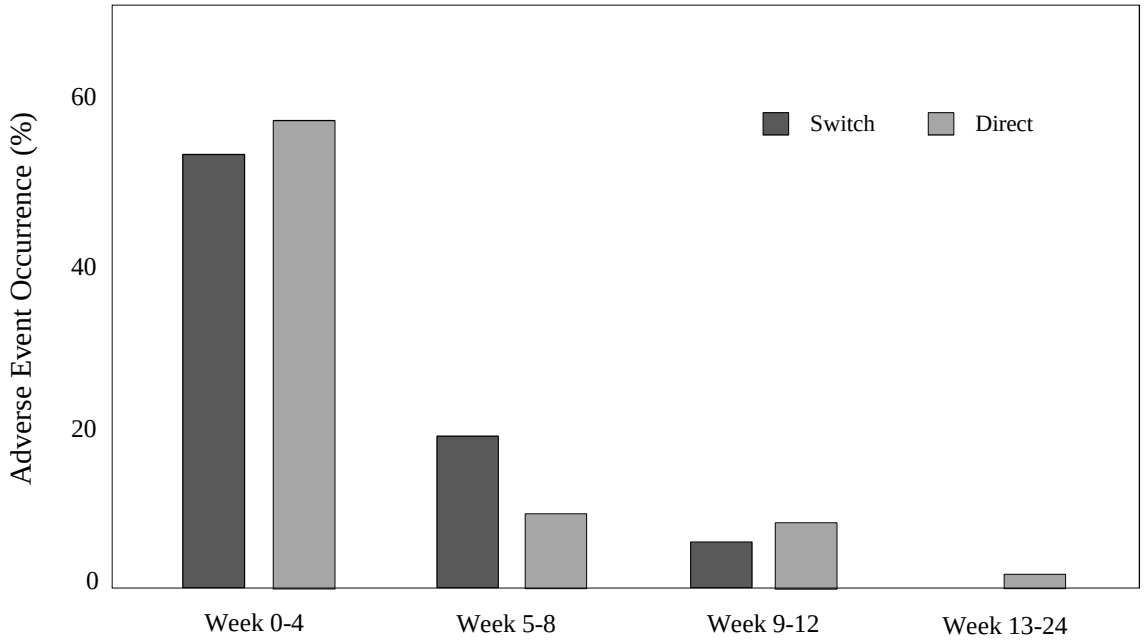
Fig.1




| | Baseline | Week 4 | Week 8 | Week 12 | Week 24 |
|---|---|---|---|---|---|
| Switch Group | 4.98 (±1.62) | 0.13 (±0.08) | 0.08 (±0.04) | 0.08 (±0.04) | 0.11 (±0.06) |
| Direct Group | 5.07 (±1.76) | 0.17 (±0.19) | 0.09 (±0.06) | 0.11 (±0.11) | 0.10 (±0.06) |
| P-value | .798 | .189 | .262 | .056 | .668 |

mean (±SD), Student's t-test

Fig.2




| | Week 0-4 | Week 5-8 | Week 9-12 | Week 13-24 |
|---|---|---|---|---|
| *Number of patients* | | | | |
| Switch Group | 25/47 (53.2) | 9/47 (19.1) | 3/47 (6.4) | 0/42 (0.0) |
| Direct Group | 31/54 (57.4) | 5/54 (9.3) | 4/51 (7.8) | 2/51 (3.9) |
| P Value | .671 | .151 | .999 | .499 |
| *Cumlative number* | | | | |
| Switch Group | 25/47 (53.2) | 34/47 (72.3) | 37/47 (78.7) | 37/42 (88.1) |
| Direct Group | 31/54 (57.4) | 36/54 (66.7) | 40/51 (78.4) | 42/51 (82.4) |
| P Value | .671 | .538 | .972 | .441 |

number/total number (%), Chi-square test or Fisher's exact test

Table1. Baseline characteristics of study patients (n=101)

| Characteristics | | Switch Group (n=47) | Direct Group (n=54) | P‡ |
|---|---|---|---|---|
| Age* (y) | | 76.3±6.87 | 75.0±5.97 | .318 |
| Testosterone* (ng/mL) | | 4.98±1.62 | 5.07±1.76 | .798 |
| PSA* (ng/mL) | | 46.72±123.26 | 52.37±85.62 | .793 |
| Gleason score | 5 or 6 | 9 (19.1%) | 10 (18.5%) | .290 |
| | 7 | 16 (34.0%) | 11 (20.4%) | |
| | 8-10 | 22 (46.8%) | 32 (59.3%) | |
| | unknown | 0 (0.0%) | 1 (1.9%) | |
| Clinical stage# | T1-2 | 34 (72.3%) | 35 (64.8%) | .609 |
| | T3 | 12 (25.5%) | 15 (27.8%) | |
| | T4 | 1 (2.1%) | 3 (5.6%) | |
| | Tx | 0 (0.0%) | 1 (1.9%) | |
| Clinical stage# | N0 | 39 (83.0%) | 45 (83.3%) | .817 |
| | N1 | 6 (12.8%) | 6 (11.1%) | |
| | Nx | 2 (4.3%) | 3 (5.6%) | |
| Clinical stage# | M0 | 35 (74.5%) | 41 (75.9%) | .828 |
| | M1 | 10 (21.3%) | 13 (24.1%) | |
| | Mx | 2 (4.3%) | 0 (0.0%) | |
| Performance status§ | 0 | 44 (93.6%) | 48 (88.9%) | .282 |
| | 1 | 2 (4.3%) | 6 (11.1%) | |
| | unknown | 1 (2.1%) | 0 (0.0%) | |

*values are means±standard deviation

† Total serum testosterone at initial diagnosis

# UICC (Union for International Cancer Control) TNM classification[5]

§ ECOG (Eastern Cooperative Oncology Group) performance status[6]

Table 2. Percent of patients with serum testosterone levels ≤0.50 ng/mL.

| Weeks | Switch-group | | | Direct-group | | |
|---|---|---|---|---|---|---|
| | N | n | % | N | n | % |
| Week 4 | 47 | 47 | 100.0 | 54 | 53 | 98.1 |
| Week 8 | 47 | 47 | 100.0 | 53 | 53 | 100.0 |
| Week 12 | 47 | 47 | 100.0 | 52 | 51 | 98.1 |
| Week 24 | 37 | 37 | 100.0 | 46 | 46 | 100.0 |

N: number of patients for whom serum testosterone level was determined

n: number of patients with serum testosterone level ≤0.50 ng/mL

Table 3. PSA levels before and after treatment

| | Switch Group | | Direct Group | | |
|---|---|---|---|---|---|
| Weeks | N | PSA* | N | PSA | P† |
| Baseline | 46 | 46.72±123.26 | 50 | 52.37±85.62 | 0.793 |
| Week 4 | 46 | 8.99±34.19 | 49 | 8.53±20.62 | 0.937 |
| Week 8 | 46 | 4.60±21.99 | 50 | 2.18±5.99 | 0.454 |
| Week 12 | 46 | 2.26±8.97 | 48 | 1.34±4.38 | 0.528 |
| Week 24 | 40 | 1.01±4.44 | 48 | 0.91±3.02 | 0.902 |

PSA, prostate-specific antigen, mean±standard deviation ng/mL

†Student’s t-test.

Table 4. Summary of adverse events ≥5% in either group

| | Switch-group (n=47) | | | | Direct-group (n=54) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1-2 | | Grade 3 | | Grade 1-2 | | Grade 3 | |
| Adverse Events | n | % | n | (%) | n | % | n | % |
| Hot flushes | 7 | 14.9 | | | 10 | 18.5 | | |
| Sweating | 2 | 4.3 | | | 7 | 13.0 | | |
| WBC decreased | 5 | 10.6 | | | 6 | 11.1 | | |
| RBC decreased | 13 | 27.7 | | | 16 | 29.6 | | |
| Platelets decreased | 3 | 6.4 | | | 4 | 7.4 | | |
| Hemoglobin decreased | 12 | 25.5 | | | 16 | 29.6 | | |
| Hematocrit decreased | 16 | 34.0 | | | 19 | 35.2 | | |
| AST increased | 4 | 8.5 | | | 12 | 22.2 | 1 | 1.9 |
| ALT increased | 5 | 10.6 | | | 6 | 11.1 | 1 | 1.9 |
| γ-GTP increased | 4 | 8.5 | | | 5 | 9.3 | | |
| LDH increased | 11 | 23.4 | | | 15 | 27.8 | | |
| ALP increased | 6 | 12.8 | | | 7 | 13.0 | 1 | 1.9 |
| Creatinine increased | 6 | 12.8 | | | 2 | 3.7 | | |

WBC, white blood cell count; RBC, red blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase