# Abiraterone versus bicalutamide in combination with gonadotropin releasing hormone antagonist therapy for high risk metastatic hormone sensitive prostate cancer.

**Takashi Ueda** ( t-ueda@koto.kpu-m.ac.jp )
Kyoto Prefectural University of Medicine
**Takumi Shiraishi**
Kyoto Prefectural University of Medicine
**Saya Ueda**
Kyoto Prefectural University of Medicine
**Motoharu Ohashi**
Kyoto Prefectural University of Medicine
**Toru Matsugasumi**
Kyoto Prefectural University of Medicine
**Yasuhiro Yamada**
Kyoto Prefectural University of Medicine
**Atsuko Fujihara**
Kyoto Prefectural University of Medicine
**Fumiya Hongo**
Kyoto Prefectural University of Medicine
**Koji Okihara**
Kyoto Prefectural University of Medicine
**Osamu Ukimura**
Kyoto Prefectural University of Medicine

**Research Article**

**Keywords:** abiraterone, bicalutamide, gonadotropin-releasing hormone antagonist, high risk metastatic hormone sensitive prostate cancer

**Posted Date:** March 5th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-269640/v1

# Abstract

### Objectives

To compare the efficacy of abiraterone with that of bicalutamide in combination with gonadotropin-releasing hormone antagonist treatment for high risk metastatic hormone-sensitive prostate cancer patients.

### Methods

One hundred and forty-nine patients with high risk metastatic hormone-sensitive prostate cancer at our hospital and affiliated hospitals between December 2013 and July 2020 were retrospectively identified. Fifty patients were administered abiraterone (1000mg/day) plus prednisolone (5mg/day) with gonadotropin-releasing hormone antagonist (degarelix) (group A) and 99 patients were administered bicalutamide (80mg/day) with gonadotropin-releasing hormone antagonist (group B).

### Results

PSA- progression-free survival of group A was significantly longer than that of group B. Abiraterone therapy and Gleason score were significant independent factors for PSA-progression-free survival. By propensity score matching, total 56 matched patients were obtained. PSA-PFS ($p<0.001$) and OS ($p=0.0071$) of high risk mHNPC patients were significantly longer in abiraterone group of matched patients. Abiraterone therapy and Gleason score were still shown to be significant independent factors for PSA-PFS in matched patients.

### Conclusions

PSA-progression-free survival and overall survival in patients who were treated with abiraterone in combination with gonadotropin releasing hormone antagonist were significantly better than those of bicalutamide.


# Introduction

Though prostate cancer today tends to be diagnosed at early stage due to the introduction of PSA screening, some patients with prostate cancer still present metastasis at the time of diagnosis in Japan [12]. Androgen deprivation therapy (ADT) as systemic therapy is generally accepted as a standard of care for patients with metastatic hormone-sensitive prostate cancer (mHSPC). In Japanese clinical practice guideline for prostate cancer, combined androgen blockade (CAB) therapy, which involves concurrent use of a gonadotropin-releasing hormone (GnRH) agonist and first-generation antiandrogen such as bicalutamide is recommended as the standard first-line therapy for metastatic prostate cancer. On the other hand, CAB therapy is not recommended in National Comprehensive Cancer Network guidelines and European Association of Urology guidelines [3].

Recently, hormonal therapy using abiraterone, next-generation antiandrogen, was reported to improve overall survival (OS) and radiographic progression-free survival (PFS) in men with high risk mHSPC who exhibit at least two of the three following factors: 8 or more Gleason score, 3 or more bone lesions, and the presence of visceral metastasis [4]. Though the superiority of abiraterone plus prednisone with GnRH agonist to placebo with GnRH agonist for treatment of high risk mHSPC had been shown in the report, there are two concerns to apply this result into clinical practice in Japan. First, as stated above, most of metastatic prostate cancer patients receive CAB therapy as first-line therapy in Japan [5]. Therefore, the effectiveness of abiraterone plus prednisone with GnRH analog should be compared with that of CAB therapy using bicalutamide. Second, GnRH antagonist, degarelix, which doesn't induce a transient rise in testosterone to aggravate the symptoms, instead of GnRH agonist are becoming major component of ADT especially for those who have a high metastatic burden in Japan [6]. However, there has been no reports to compare the efficacy of abiraterone with that of bicalutamide in combination with GnRH antagonist treatment for high risk mHSPC.

The aim of this study was to compare the efficacy of abiraterone with that of bicalutamide in combination with GnRH antagonist treatment for high risk mHSPC.

# Methods

## Patients and Treatments

We retrospectively identified 149 patients with high risk mHSPC at our hospital and affiliated hospitals in KPUM-Prostate Cancer Study Group between December 2013 and July 2020. All patients have two or more following factors: 8 or more Gleason score, at least three bone lesions, and the presence of visceral metastasis. Fifty patients were administered abiraterone (1000mg/day) plus prednisolone (5mg/day) with GnRH antagonist (degarelix) (group A). Ninety-nine patients who were administered bicalutamide (80mg/day) with GnRH antagonist were categorized as group B.

Bone and visceral metastasis were assessed by bone scintigraphy and computed tomography (CT). Extent of disease (EOD) score was measured by bone scintigraphy. This study was approved by the institutional review board of Kyoto Prefectural University of Medicine (ERB-C-1071-2) and each affiliated hospitals and conducted in compliance with the Declaration of Helsinki. The institutional review board waived individual written informed consent due to the retrospective nature of this study.

## Statistical Analysis

The chi-square test and Wilcoxon's rank sum test was used to compare the two groups as appropriate. Kaplan-Meier analysis was used for estimation of the differences in time events between the two groups using the log-rank test. Cox's proportional hazard models were applied to investigate factors associated with progression free survival. Propensity score matching technique was used to adjust the clinical backgrounds between two groups. Statistical analyses were performed using SAS JMP, Version 14, and $P<0.05$ was taken to indicate statistical significance.

# Results

### Clinical background of the patients

Table 1 shows clinical background of the patients. Fifty patients were administered abiraterone plus prednisolone with GnRH antagonist (degarelix) (group A). Ninety-nine patients were administered bicalutamide with GnRH antagonist (group B). There were no significant differences between group A and group B in terms of pretreatment PSA (p=0.554). The patients of group A was significantly younger than those of group B (p<0.001). Pretreatment ALP level, Gleason score and EOD score of group A were significantly higher than those of group B (p=0.0411, 0.0439 and 0.0402), indicating that patients of group A have more advanced and aggressive disease compared to those of group B. The significant shorter observation period of group A (p<0.001) was probably due to the late approval of abiraterone in Japan.

### Prognostic factor of PSA progression free survival

As shown in Figure S1, PSA-PFS of group A was significantly longer than that of group B. It has been reported that age, pretreatment PSA level, Gleason score, EOD score and pretreatment ALP level were prognostic factors associated with PSA control in mHNPC treatment [78]. Therefore, we performed Cox Logistic regression analysis to investigate factors associated with PSA-PFS in patients with high risk mHSPC using variables of those factors in addition to antiandrogen use (abiraterone or bicalutamide). Abiraterone therapy and Gleason score were shown to be significant independent factors for PSA-PFS in high risk mHNPC treatment (Table. 2). However, OS of high risk mHNPC was not significantly different between two groups (Figure S2).

### The difference of effectiveness between abiraterone and bicalutamide for high risk mHNPC patients adjusted by propensity score matching technique.

Because several factors associated with PSA-PFS and OS were significantly different between two groups (group A and B) (Table1), we next used propensity score matching technique to adjust these clinical backgrounds between two groups to examine the difference for high risk mHNPC patients more precisely. Total 56 matched patients were obtained from 149 patients. As described in Table 3, clinical backgrounds were well adjusted between the two groups. PSA-PFS (p<0.001) and OS (p=0.0071) of high risk mHNPC patients were significantly longer in abiraterone group of matched patients (Fig.1 and 2). Abiraterone therapy and Gleason score were still shown to be significant independent factors for PSA-PFS in matched patients (Table 4).

# Discussion

In this study we retrospectively compared the efficacy of abiraterone with that of bicalutamide in combination with GnRH antagonist treatment for high risk mHNPC and found that PSA-PFS and OS in patients who were treated with abiraterone were significantly better than those of bicalutamide.

In western countries, CAB therapy is rarely used as the standard first-line therapy for metastatic prostate cancer, while in Japan it has been widely accepted since several previous reports had suggested that Japanese prostate cancer patients respond to CAB therapy more effectively than other races [9]. For example, it is reported that the adjusted prostate cancer-specific mortality in Japanese prostate cancer patients who received CAB therapy is less than half of those in USA patients [10]. Several reasons such as genetic and dietary/environmental factors have been discussed to explain the discrepancy between countries [11]. Furthermore, the difference in typical dosage of bicalutamide (80mg/day in Japan vs 50mg in western countries) has also been accounted for the controversial results [12]. In fact, another report has also suggested that the dose of bicalutamide is associated with PSA response [13]. In another study, Mathew RC et al. reported that CAB therapy improved survival more significantly compared to LH-RH monotherapy in men with very-high-risk metastatic disease, but not with lower risk metastatic tumors, indicating that CAB therapy may be more effective especially in high risk metastatic disease than low risk metastatic disease [10]. One of the most important points in the current study is that we showed the superiority of abiraterone use compared to 80mg use of bicalutamide in Japan where these drugs are often selected for the treatment of patients with high risk mHSPC in the real clinical setting.

Bertrand et al suggested that GnRH antagonist, degarelix, may be more effective than GnRH agonist, leuprolide, as for PSA control [14]. Furthermore, Kashiwabara et al reported that GnRH antagonist was more effective than GnRH agonist for CAB treatment of bone metastatic prostate cancer with pretreatment PSA level ≥ 50ng/ml [6]. There are several hypotheses about the reason why GnRH antagonist treatment exhibits better outcome than GnRH agonist treatment. Previous report suggested that GnRH antagonist treatment decreases PSA levels at a faster pace than GnRH agonist [14]. This rapid effect may result in better tumor control for longer duration. From these reasons, GnRH antagonist, instead of GnRH agonist, are widely used for ADT in Japan. Currently, almost all patients who had been diagnosed as high risk mHSPC in our hospital also received GnRH antagonist instead of GnRH agonist. In the present study the PSA level decreased rapidly in both of agonist and antagonist groups and average PSA response rate after 3 months of treatment was 99% in the two groups (data not shown). Comparison of PSA-PFS and OS between GnRH agonist and antagonist in CAB therapy may be future work. GnRH receptor expression has been reported in various types of malignant cells including prostate cancer cells [1516]. It is reported that both GnRH agonist and antagonist decrease proliferation of prostate cancer cells [17]. The *in vitro* comparison of growth suppression effect between GnRH agonist and antagonist may lead to more profound understanding of differential effect between the two drugs.

This is the first report which compared the efficacy of abiraterone with bicalutamide, in combination with GnRH antagonist for high risk mHSPC patients in Japan. However, it is important to note that there were several limitations in the present study. The patient cohort was small, and there was a significant difference regarding patient background because of the retrospective nature of the study. Moreover, observation period was short especially in patients treated with abiraterone. Therefore, a further prospective study with a larger cohort for longer period is required.

In conclusion, we demonstrated that abiraterone use in combination with GnRH antagonist instead of bicalutamide may have advantages regarding OS as well as PSA-PFS in patients with high risk mHSPC. The findings from the study could provide useful information when physicians choose a treatment plan in patients with high risk mHSPC.

# Declarations


### Acknowledgements

This report is based on the results from our hospital and affiliated hospitals. We express gratitude for cooperation of urologists in affiliated hospitals. Urologists who cooperated are: Hiroaki Miyashita, So Ushijima and Toshiya Takamura, Department of Urology, Omihachiman Community Medical Center; Jintetsu So and Yuta Inoue, Department of Urology, Japanese Red Cross Daini Hospital; Shunji Harikai and Sojiro Hirano, Department of Urology, Kyoto Yamashiro General Medical Center; Yasuhiro Yamada, Kyoto Okamoto Memorial Hospital, Department of Urology; Kento Masuda, Department of Urology, Kyoto Kuramaguchi Medical Center; Tsuyoshi Iwata, Department of Urology, Kyoto Min-Iren Chuo Hospital; Kazuya Mikami and Naruhiro Kayukawa, Department of Urology, Japanese Red Cross Daiichi Hospital; Nobuhisa Hagiwara, Department of Urology, Maizuru Medical Center; Kenji Hiraoka, Department of Urology, North Medical Center Kyoto Prefectural University of Medicine; Hirokazu Ishida, Department of Urology, Uji Takeda Hospital; Kimihiro Yano, Department of Urology, Fujinomiya City General Hospital; Akihisa Ueno, Department of Urology, Saiseikai Suita Hospital; Masakatsu Oishi, Department of Urology, Aiseikai Yamashina Hosipital; Motohiro Kanazawa and Asa Nakata, Department of Urology, Kyoto Chubu Medical Center; Naoki Hirahara and Ichiro Takeuchi, Department of Urology, Kyoto Kizugawa Hospital; Hidehisa Boku, Department of Urology, Kyoto Tanabe Central Hospital; Yusuke Gabata, Department of Urology, Ayabe City Hospital.


### Conflict of interest

The authors declare no conflict of interest.

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# Tables

**Table 1** Patient characteristics

| hormone therapy | | abiraterone+GnRH antagonist (group A)<br><br>n=50 | bicalutamide+GnRH antagonist (group B)<br><br>n=99 | A vs B<br><br>p-value |
|---|---|---|---|---|
| Median age at diagnosis years (range) | | 73.5(53-85) | 77(57-91) | <0.001 |
| Median pretreatment PSA level ng/mL | | 663.68(2.72-24201) | 357.23(4.177-32548) | 0.554 |
| Median pretreatment ALP | | 711(124-12122) | 519(126-7060) | 0.0411 |
| Pathological diagnosis | Gleason score 7 | 1 | 2 | 0.0439 |
| | Gleason score 8 | 8 | 26 | |
| | Gleason score 9 | 31 | 62 | |
| | Gleason score 10 | 9 | 9 | |
| EOD (extent of disease) score | EOD0 | 3 | 3 | 0.0402 |
| | EOD1 | 5 | 23 | |
| | EOD2 | 13 | 32 | |
| | EOD3 | 17 | 23 | |
| | EOD4 | 11 | 14 | |
| Median observation period months (range) | | 10.5(3-23) | 23(3-88) | <0.001 |

**Table 2** Multivariate analysis for PSA-PFS

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p-vslue | HR | 95% CI | p-value |
| abiraterone therapy | 4.64 | 2.31-9.31 | <0.001 | 7.53 | 3.48-16.30 | <0.001 |
| age at diagnosis years | 1.89 | 0.60-6.07 | 0.28 | 0.42 | 0.12-1.55 | 0.19 |
| pretreatment PSA level | 1.12 | 0.11-5.55 | 0.91 | 0.93 | 0.039-6.71 | 0.95 |
| Gleason score | 4.79 | 1.71-13.90 | 0.0035 | 17.99 | 3.73-52.10 | 0.0001 |
| EOD (extent of disease) score | 1.68 | 0.78-3.64 | 0.18 | 0.282 | 0.57-4.27 | 0.40 |
| pretreatment ALP level | 1.32 | 0.29-4.45 | 0.69 | 19.027 | 0.26-9.46 | 0.51 |

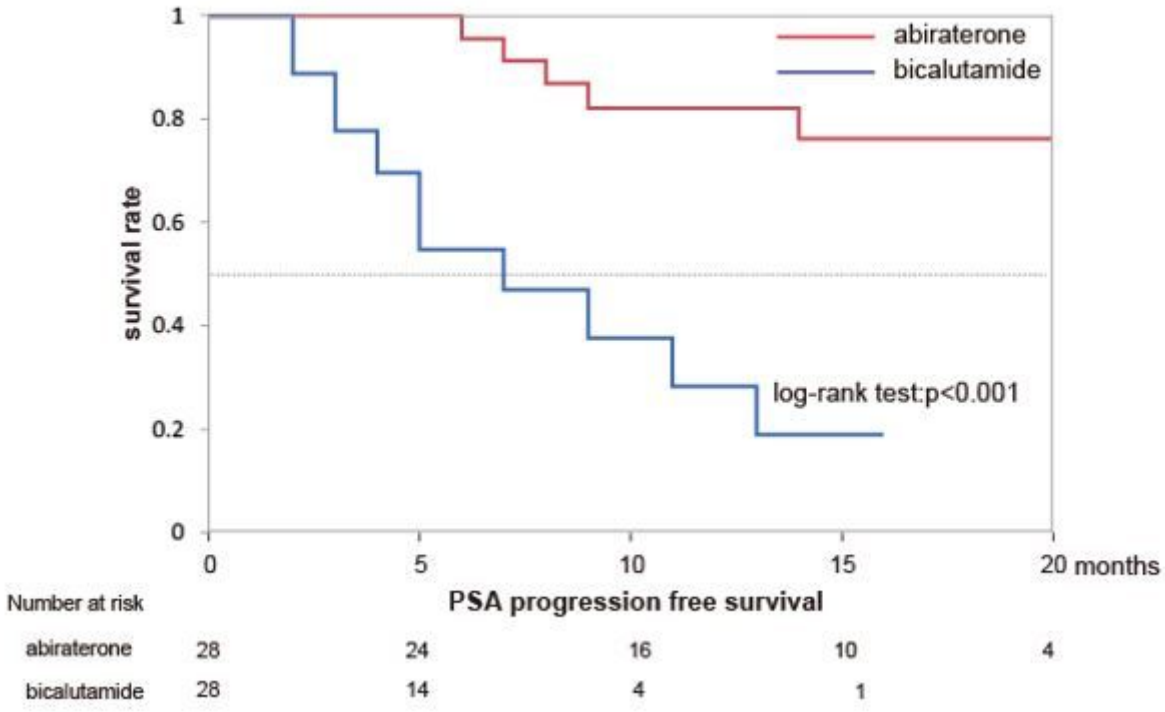
**Table 3** Characteristics of matched patients (group A and Group B)

| hormone therapy | | abiraterone+GnTH antagonist (Group A) n=28 | bicaltamide+GnRH antagonist (Group B) n=28 | A vs B p-value |
|---|---|---|---|---|
| Median age at diagnosis years (range) | | 74(55-84) | 76(57-86) | 0.2293 |
| Median pretreatment PSA level ng/mL | | 593.369(10.8-10559) | 289.205(4.177-32548) | 0.6462 |
| Median pretreatment ALP | | 584.5(232-3927) | 731(199-7060) | 0.6128 |
| Pathological diagnosis | Gleason score 7 | 1 | 0 | 0.5568 |
| | Gleason score 8 | 4 | 6 | |
| | Gleason score 9 | 16 | 18 | |
| | Gleason score 10 | 7 | 4 | |
| EOD (extent of disease) score | EOD0 | 1 | 0 | 0.4475 |
| | EOD1 | 3 | 6 | |
| | EOD2 | 10 | 10 | |
| | EOD3 | 7 | 8 | |
| | EOD4 | 7 | 4 | |
| Median observation period months (range) | | 14.5(2-23) | 9.5(3-31) | 0.2093 |

| | Univariate analysis | | |
|---|---|---|---|
| | HR | 95% CI | p-vslue |
| abiraterone therapy | 7.09 | 2.45-20.56 | <0.001 |
| age at diagnosis years | 0.981 | 0.99-1.00 | 0.5555 |
| pretreatment PSA level | 1.12 | 0.11-5.55 | 0.5328 |
| Gleason score | 2.48 | 1.25-5.17 | 0.0089 |
| EOD (extent of disease) score | 1.31 | 0.88-2.00 | 0.18 |
| pretreatment ALP level | 1.32 | 0.99-1.00 | 0.08 |

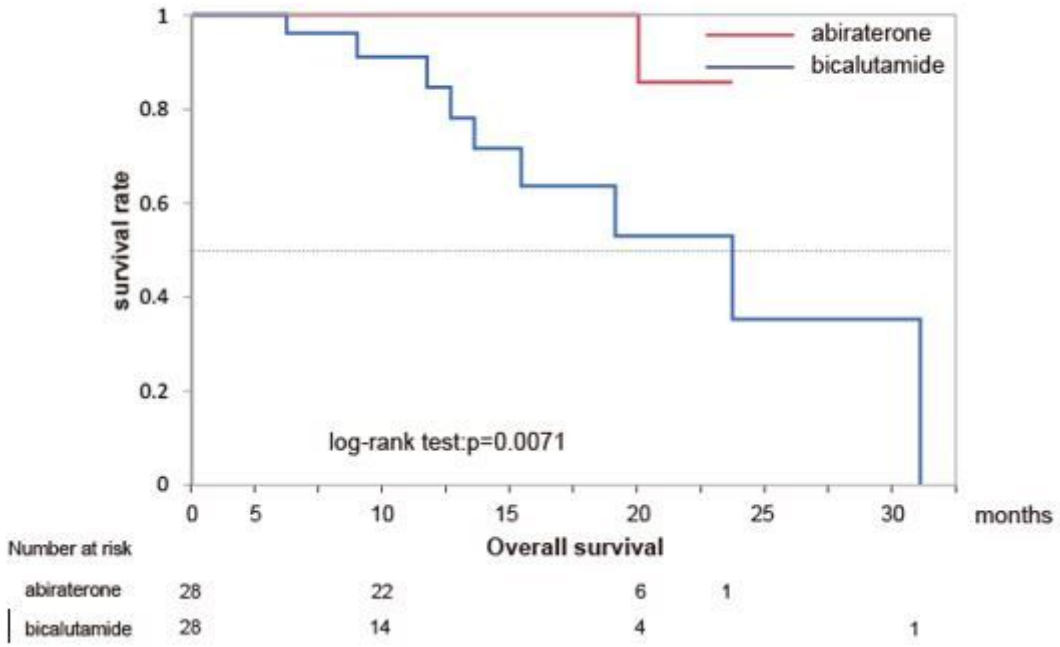
**Table 4** Univariate analysis for PSA-PFS in matched patients

# Figures




## Figure 1

Kaplan-Meire estimates of PSA progression free survival in matched patients.




## Figure 2

Kaplan-Meire estimates of overall survival in matched patients.

## Supplementary Files

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