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ORIGINAL ARTICLE

# Enzalutamide versus flutamide for castration-resistant prostate cancer after combined androgen blockade therapy with bicalutamide: a retrospective study

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## Abstract

**Background** Alternative anti-androgen therapy (AAT) with flutamide after combined androgen blockade (CAB) therapy with bicalutamide for metastatic prostate cancer is common. However, no studies have compared enzalutamide without AAT with enzalutamide after AAT with flutamide as treatment for castration-resistant prostate cancer (CRPC). We aimed to compare the efficacies of flutamide and enzalutamide for CRPC.

**Methods** In our hospital, 55 patients were diagnosed with CRPC after CAB therapy and administered flutamide or enzalutamide between May 2014 and December 2017. Patients with flutamide failure were administered enzalutamide. We evaluated the (1) prostate-specific antigen (PSA) best response with initial therapy, (2) PSA progression-free survival with initial therapy (PSA-PFS), (3) PSA best response with enzalutamide therapy, (4) PSA-PFS of enzalutamide therapy, and (5) overall survival (OS).

**Results** As first-line therapy, patients were administered enzalutamide ($n=29$) or flutamide ($n=26$). In the flutamide group, 18 patients showed disease progression and were administered enzalutamide. PSA best response was statistically higher in the enzalutamide group. PSA-PFS was significantly longer in the enzalutamide group [hazard ratio (HR) 0.42, 95% confidence interval (CI) 0.19–0.92, $p=0.024$]. However, there was no significant difference in PSA best response with enzalutamide therapy and PSA-PFS between the first- and second-line enzalutamide therapies (HR 0.80, 95% CI 0.33–1.94, $p=0.62$). There was no significant difference in OS between enzalutamide and flutamide groups (HR 1.85, 95% CI 0.53–6.42, $p=0.33$).

**Conclusions** AAT with subsequent flutamide after CAB therapy with bicalutamide may be suitable for some CRPC patients.

**Keywords** Castration-resistant prostate cancer · Enzalutamide · Flutamide

## Introduction

Prostate cancer is the most commonly diagnosed cancer and is the third leading cause of cancer-related deaths among men worldwide [1]. In most patients who are treated for advanced recurrent prostate cancer with androgen-deprivation therapy (ADT) that comprises a luteinizing hormone-releasing hormone (LHRH) analog or orchiectomy, with or without an anti-androgen, disease progression occurs despite effective suppression of serum testosterone. These patients

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are then diagnosed with castration-resistant prostate cancer (CRPC).

In Asia, including Japan, combined androgen blockade (CAB) therapy using an LHRH analog with an anti-androgen is more widely used than LHRH analog monotherapy, because CAB therapy is reported to be superior to ADT without an anti-androgen in terms of long-term efficacy among Japanese patients with prostate cancer [2]. Therefore, the majority of Japanese patients with advanced prostate cancer are treated with CAB and are diagnosed with CRPC by prostate-specific antigen (PSA) recurrence with or without confirming anti-androgen withdrawal syndrome (AWS). Alternative anti-androgen therapy (AAT) with flutamide, subsequent to CAB therapy with bicalutamide, was widely used before the androgen receptor-targeted therapy (ART) era, particularly in Japan [3–8]. The response rate of AAT, defined as a decrease of > 50% from the baseline serum PSA level, was 22%, and patients who respond to AAT have been reported to have good prognosis [4]. This phenomenon is attributed to the different mechanism of actions among anti-androgens [7]. Indeed, we have experienced long-lasting effective cases by AAT in clinical practice.

Flutamide, a non-steroidal oral anti-androgen, was often used in clinical practice before bicalutamide was approved. Some small, single-arm non-randomized studies suggest a PSA benefit when flutamide is used as the second-line hormonal therapy [3–9]. However, the use of flutamide is optional for limited patients with CRPC according to the American Urological Association guidelines [10] owing to the modest PSA benefit, with PSA decline of > 50% occurring typically in only 20–40% of men with a median duration measured in several months.

Enzalutamide is an androgen receptor inhibitor that targets several steps in the androgen receptor signaling pathway. It inhibits the binding of androgens to the androgen receptor, androgen receptor nuclear translocation, and androgen receptor-mediated DNA binding [11]. In preclinical studies, enzalutamide showed a higher affinity for the androgen receptor and superior suppression of key components of the androgen receptor signaling pathway than bicalutamide [11, 12]. Subsequently, enzalutamide was approved for the treatment of metastatic CRPC based on the results of two pivotal placebo-controlled phase III trials, namely, AFFIRM [13] and PREVAIL [14].

Before the ART era, the treatment options for CRPC were limited, and AAT with flutamide has been widely used in Asia, including Japan. According to the post hoc analyses of the PREVAIL study, 40% of east Asian patients (50% of Japanese patients) were administered two prior anti-androgen drugs, which are bicalutamide and flutamide [15, 16]. However, no clinical studies have compared enzalutamide without AAT (early group) with enzalutamide after AAT with flutamide (deferred group) as treatment modalities for CRPC. Moreover, there is no evidence of the superiority of enzalutamide to AAT in terms of efficacy, and the comparison between enzalutamide and enzalutamide after AAT would be meaningful. Thus, we aimed to compare enzalutamide without AAT with enzalutamide after AAT with flutamide for CRPC after CAB therapy with bicalutamide.

## Materials and methods

### Study population

Records of 94 CRPC patients treated in Osaka City University Hospital, Osaka, Japan, between May 2014 and December 2017 were reviewed. All the patients were histologically diagnosed as having prostate cancer and underwent CAB therapy with 80 mg bicalutamide and luteinizing hormone-releasing hormone agonist/antagonist as initial hormonal therapy. They were also diagnosed with CRPC on the basis of biochemical or radiographic progression with serum testosterone level < 50 ng/dL despite undergoing CAB therapy. A total of 55 CRPC patients met the eligibility criterion of no prior treatment with enzalutamide, flutamide, abiraterone, or chemotherapy after CAB therapy.

### Treatment

The patients were treated with enzalutamide (160 mg/day, 4 × 40 mg capsules once daily) or flutamide (375 mg/day; 3 × 125 mg tablets thrice daily) depending on the patients' preference and doctor's decision. The dose of the treatment drug can be reduced according to the adverse effects (enzalutamide: 120 mg/day, flutamide: 250 mg/day). The treatment was changed in case of intolerable adverse effects, which may result in difficulty in continuing the medication, or disease progression, defined as PSA progression, radiographic progression, or worsening of symptoms. The flutamide treatment was changed if the patient had PSA progression, and enzalutamide was the primary drug for the subsequent treatment of patients treated with flutamide.

### Evaluation

Patients were evaluated on the basis of the following outcomes:

1. *PSA response rate at 3 and 6 months* PSA response was defined as PSA decrease of ≥ 50% from the baseline. If the initial enzalutamide therapy was switched to other treatments due to disease progression before 3 or 6 months, such cases were regarded as "non-responders", regardless of the efficacy of the subsequent treatment. In addition, the PSA response rate in patients in

whom flutamide was switched to enzalutamide was calculated to determine the efficacy of enzalutamide in the flutamide-to-enzalutamide cohort.
2. *PSA best response* PSA best response was defined as the maximum PSA decreased rate from baseline.
3. *PSA progression-free survival*: PSA progression-free survival (PSA-PFS) of enzalutamide or flutamide was calculated.
4. *Time to treatment failure with initial therapy* Time to treatment failure with initial therapy (TTF) was defined as the time from the start of initial therapy to treatment failure of initial therapy.
5. *PSA progression-free survival of enzalutamide therapy* PSA progression-free survival of enzalutamide therapy (PSA-PFS-Enz) was defined as PSA-PFS of the first-line enzalutamide therapy or second-line enzalutamide therapy, as the subsequent treatment of flutamide.
6. *Time to treatment failure with enzalutamide* Time to treatment failure with enzalutamide (TTF-Enz) was defined as the time from the start of initial therapy to treatment failure with enzalutamide. If the initial flutamide therapy was continued, the patients were considered to have not failed the treatment with enzalutamide.
7. *Overall survival* Deaths from any cause comprise the overall survival (OS) events.
8. *Subsequent life-prolonging therapy* Information regarding initiation of subsequent prostate cancer therapies was collected.
9. *Safety* Information on all the adverse effects due to the treatment drug was collected.

All clinical assessments of disease progression were defined according to the Prostate Cancer Clinical Trials Working Group (PCWG2) criteria [17].

### Ethical consideration

This study was approved by the Institutional Review Board of Osaka City University Hospital (Reference number: 3109). Given that this study was an observational study, we did not obtain consent directly from the patients, but did guarantee the opportunity by opt-out.

### Statistical analysis

Differences in categorical parameters were assessed using the Student's *t* test. Cumulative rates were estimated using the Kaplan–Meier method, and the significance of differences between curves was tested by the log-rank test. A value of $p < 0.05$ was considered statistically significant. All the data were analyzed using Prism 7 (GraphPad Software, La Jolla, CA, USA).

## Results

### Patients' characteristics

All the 55 patients in this study were treated with bicalutamide as CAB therapy before the diagnosis of CRPC. For the first-line therapy of CRPC, 29 patients were treated with enzalutamide, whereas 26 patients were treated with flutamide. Among these patients, baseline demographic and disease characteristics were not significantly different between the enzalutamide and flutamide treatment groups (Table 1). Of the 26 patients treated with flutamide, 18 patients were confirmed to have disease progression and were treated with enzalutamide as a subsequent therapy.

Regarding the patients' characteristics, our cohort had lower body weight and body mass index and higher percentage of ECOG performance status (PS) of 0 than the PREVAIL cohort. In terms of disease characteristics, our cohort had lower median PSA level at baseline, had Gleason score of 8 or higher, and had fewer prior radical prostatectomy or radiation therapy than the PREVAIL cohort, and we included the patients without metastases (15%). These characteristics are common in Japanese CRPC patients in clinical practice.

### PSA response rate at 3 and 6 months

Of the 29 patients treated with enzalutamide as first-line therapy, 25 and 23 patients had PSA response, indicating that PSA decreased by ≥ 50% from baseline at 3 and 6 months, respectively. In contrast, of the 26 patients treated with flutamide, 8 and 1 patient had PSA response at 3 and 6 months, respectively (Table 2). However, 14 and 11 patients who underwent second-line enzalutamide therapy after flutamide had PSA response at 3 and 6 months, respectively. The PSA response of the first-line therapy at 3 and 6 months were statistically higher in the patients treated with enzalutamide, but there was no significant difference in the PSA response of enzalutamide therapy between the first- and second-line therapies (Table 3).

### PSA best response

Of the 29 patients who underwent first-line enzalutamide therapy, 25 patients had ≥ 50% PSA response at their PSA best response, whereas 12 in the 26 patients treated with flutamide had ≥ 50% PSA response at their PSA best response. The PSA best response was statistically higher in the patients treated with enzalutamide (Fig. 1a). However,

**Table 1** Baseline patient and disease characteristics

| | Enzalutamide ($n=29$) | Flutamide ($n=26$) | $p$ value |
|---|---|---|---|
| Median age (years) | 75 (53–91) | 78 (63–92) | 0.13 |
| Median body weight (kg) | 62 (49–97) | 63 (36–78) | |
| Median body mass index (kg/m$^2$) | 23 (20–31) | 23 (13–30) | |
| Initial PSA (ng/mL) | 249 (8.8–8835) | 68 (6.7–3254) | 0.09 |
| Duration of CAB therapy | 22.9 (6.9–92.2) | 31.5 (9.7–158) | 0.18 |
| PSA at first-line therapy for CRPC | 8.9 (1.1–172) | 3.2 (0.4–330) | 0.61 |
| Median observation period (months) | 16.8 (3.0–48.9) | 25.8 (5.8–52.9) | 0.27 |
| Gleason score ≥ 8 at initial diagnosis (%) | 24 (83%) | 24 (92%) | 0.43 |
| ECOG PS = 0 (%) | 23 (79%) | 19 (73%) | |
| ECOG PS ≧ 2 (%) | 2 (7%) | 1 (4%) | |
| Prior CAB therapies with bicalutamide (%) | 29 (100%) | 26 (100%) | |
| Prior radical prostatectomy (%) | 0 (0%) | 1 (4%) | |
| Prior radiation therapy (%) | 5 (17%) | 2 (8%) | 0.43 |
| nmCRPC | 4 (14%) | 4 (15%) | 0.43 |

*PSA* prostate-specific antigen, *CAB* combined androgen blockade; *CRPC* castration-resistant prostate cancer, *PS* performance status, *nmCRPC* nonmetastatic castration-resistant prostate cancer

**Table 2** PSA response rate at 3 and 6 months and PSA best response of each therapy

| PSA response rate | First-line enzalutamide ($n=29$) | First-line flutamide ($n=26$) | $p$ value |
|---|---|---|---|
| 3 months | 25 (86%) | 8 (31%) | < 0.01 |
| 6 months | 23 (79%) | 1 (4%) | < 0.01 |
| Best response | 25 (86%) | 12 (46%) | < 0.01 |

*PSA* prostate-specific antigen

there was no difference in the PSA best response between the first- and second-line enzalutamide therapies (Fig. 1b).

## PSA-PFS

PSA-PFS of the first-line therapy in the enzalutamide treatment group was significantly longer than that in the flutamide treatment group (median 21.2 and 8.6 months, respectively; HR 0.42, 95% CI 0.19–0.92, $p=0.024$) (Fig. 2a).

## Time to treatment failure with initial therapy (TTF)

TTF in the enzalutamide treatment group was significantly longer than that in the flutamide treatment group (median 22.6 and 8.4 months, respectively; HR 0.39, 95% CI 0.19–0.82, $p=0.009$) (Fig. 2b).

## PSA progression-free survival of enzalutamide therapy (PSA-PFS-Enz)

There was no significant difference in PSA-PFS-Enz between the first- and second-line therapies following flutamide (median 21.2 and 14.9 months, respectively; HR 0.80, 95% CI 0.33–1.94, $p=0.62$) (Fig. 3A).

## Time to treatment failure with enzalutamide (TTF-Enz)

There was no significant difference in TTF-Enz between the first-line enzalutamide therapy and sequential therapy of flutamide-to-enzalutamide (median 22.6 and 35.4 months, respectively; HR 1.46, 95% CI 0.62–3.47, $p=0.38$) (Fig. 3b).

**Table 3** PSA response rate at 3 and 6 months and PSA best response of enzalutamide therapy

| | First-line enzalutamide | Second-line enzalutamide | $p$ value |
|---|---|---|---|
| PSA response rate at 3 months | 25/29 (79%) | 14/18 (78%) | 0.69 |
| PSA response rate at 6 months | 18/23 (78%) | 11/14 (79%) | 1.00 |
| PSA response rate (best response) | 25/29 (79%) | 17/18 (94%) | 0.64 |

*PSA* prostate-specific antigen

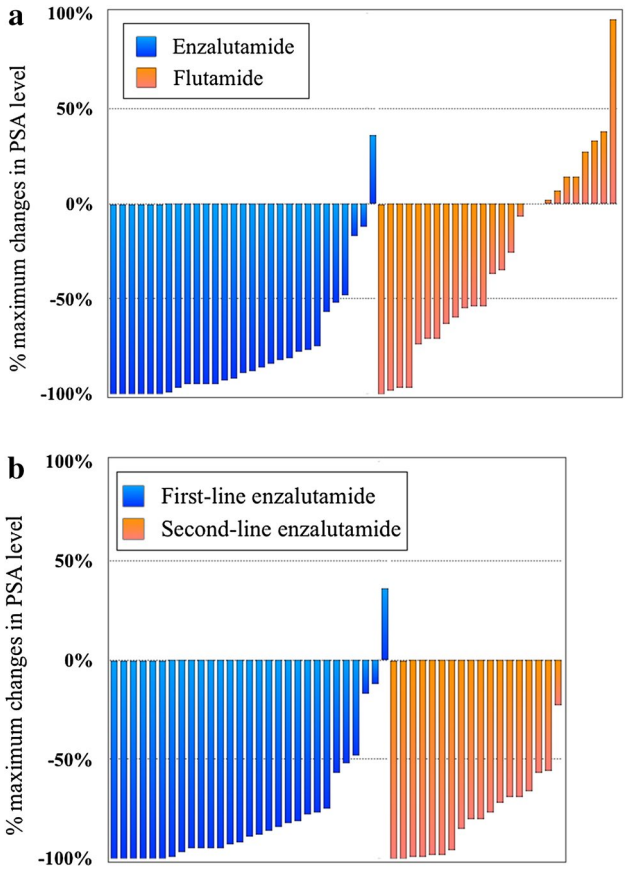


**Fig. 1** PSA best response. **a** Enzalutamide and flutamide as first-line therapies for CRPC. **b** Enzalutamide as first- and second-line therapies after flutamide therapy. *PSA* prostate-specific antigen; *CRPC* castration-resistant prostate cancer

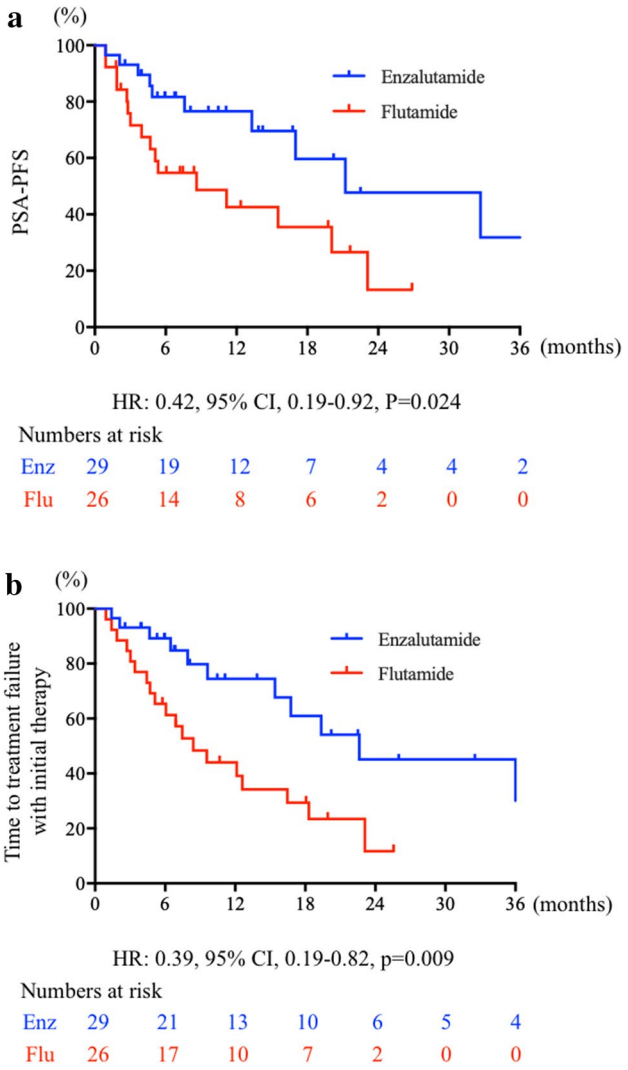


**Fig. 2** **a** PSA progression-free survival of the first-line therapy for CRPC. **b** Time to treatment failure with initial therapy for CRPC. *PSA* prostate-specific antigen, *CRPC* castration-resistant prostate cancer

## OS

There was no significant difference in OS between the first-line enzalutamide therapy and sequential therapy of flutamide-to-enzalutamide (median not reached in both groups; HR 1.85, 95% CI 0.53–6.42, $p = 0.33$) (Fig. 4).

## Subsequent life-prolonging therapy

At the data cut, 17 of the 29 patients in the enzalutamide group continued taking enzalutamide and 8 of the 26 patients in the flutamide group continued taking flutamide. All the patients who had progression with flutamide were administered enzalutamide as second-line therapy. Those who had progression with enzalutamide were administered abiraterone, docetaxel, cabazitaxel radium-223, and other hormonal drugs (Table 4). There was no significant difference in the subsequent life-prolonging therapy between the two groups.

## Safety

Adverse events are summarized in Table 5. Flutamide had a favorable safety profile as described in a previous report [18] and flutamide was discontinued for two patients because of appetite loss and diarrhea. Enzalutamide also had a favorable safety profile similar to that in the PREVAIL study in which enzalutamide was discontinued for two patients because of appetite loss and taste disorder [14]. Of 47 patients treated using first-line or second-line enzalutamide, the enzalutamide dose was reduced to 120 mg/day in 26 patients because of adverse effects; however, all the adverse effects ameliorated or disappeared after dose reduction.

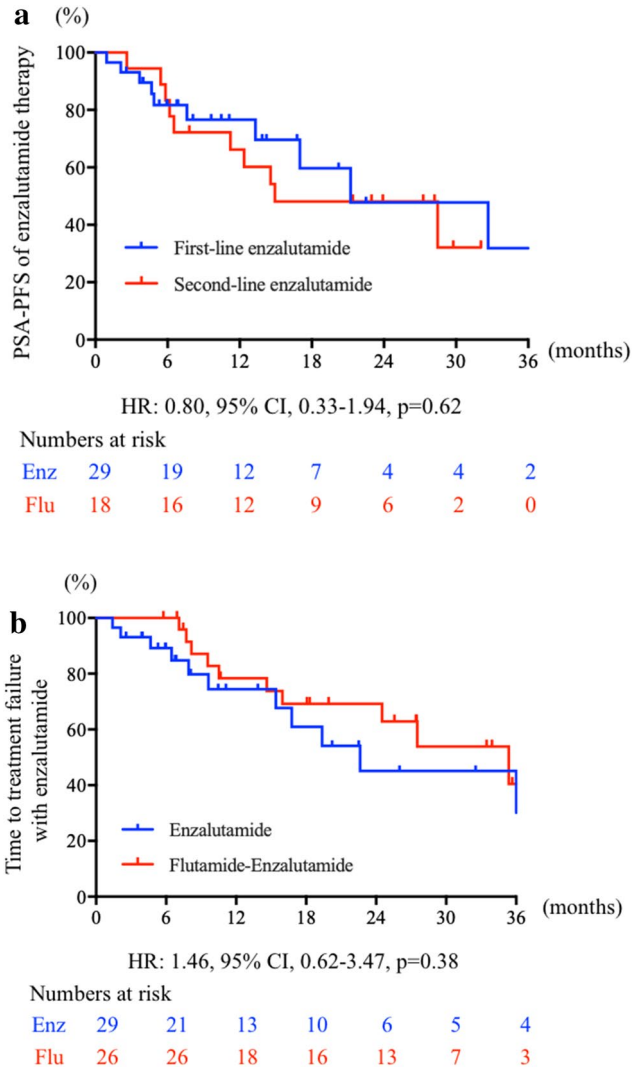


**Fig. 3** **a** PSA progression-free survival of the first- and second-line enzalutamide therapies. **b** Time to treatment failure with enzalutamide. *PSA* prostate-specific antigen

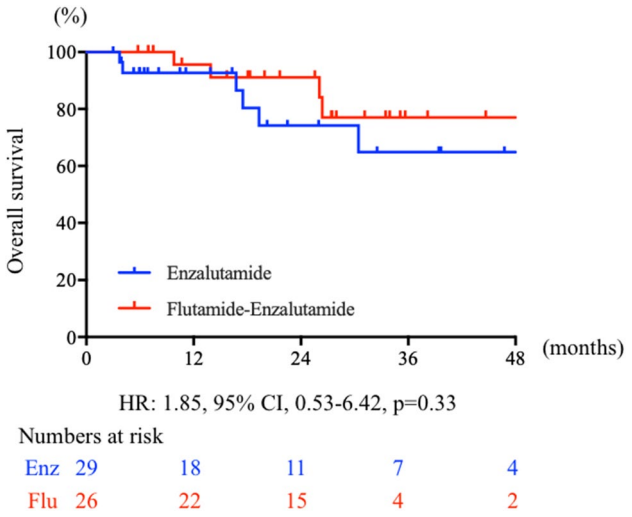


**Fig. 4** Overall survival between the first-line enzalutamide therapy and the sequential therapy of flutamide-to-enzalutamide

**Table 4** Subsequent life-prolonging therapy after initial therapy

| | Enzalutamide ($n=29$) | Flutamide ($n=26$) |
|---|---|---|
| Ongoing initial therapy | 17 | 8 |
| Any subsequent life-prolonging therapy | 12 | 18 |
| Enzalutamide | 0 | 18 |
| Abiraterone | 2 | 2 |
| Docetaxel | 5 | 4 |
| Cabazitaxel | 3 | 1 |
| Radium-223 | 3 | 1 |
| Others | 7 | 4 |

## Discussion

In Asia, including Japan, CAB therapy is widely used than the LHRH analog monotherapy among Japanese patients with prostate cancer, because CAB therapy is reported to be superior to ADT without an anti-androgen in terms of long-term efficacy [2]. The majority of Japanese patients with advanced prostate cancer are treated with CAB therapy and AAT with flutamide as the subsequent therapy for CRPC was widely used before the ART era [3–8]. After launching enzalutamide and abiraterone in 2014, ART became the first choice of treatment for CRPC instead of AAT with flutamide, but flutamide is still used widely in clinical practice because of previous experiences and economic benefits. Even after the ART era, it was reported that the duration of the initial CAB therapy was significantly correlated with PSA decline of AAT therapy [9, 19]. However, there is no evidence of the superiority of enzalutamide to AAT, and no clinical studies have compared enzalutamide without AAT with enzalutamide after AAT with flutamide as treatment modalities for CRPC.

We investigated the efficacy of enzalutamide and flutamide as first-line therapies for CRPC. In this study, enzalutamide was superior to flutamide in terms of PSA response rate at 3 and 6 months, PSA best response, PSA-PFS, and TTF as the first-line therapy for CRPC after CAB therapy with bicalutamide. As reported in STRIVE and TERRAIN studies that enzalutamide was superior to bicalutamide as the first-line therapy for CRPC after ADT, enzalutamide is revealed to be superior to old anti-androgens in clinical practice [20, 21].

We also investigated the efficiency of enzalutamide between the early and deferred groups. The efficiency of

**Table 5** Adverse events and workaround

| | First-line enzalutamide($n=29$) | | First-line flutamide($n=26$) | | Second-line enzalutamide ($n=18$) | |
|---|---|---|---|---|---|---|
| | All grades | Grade ≥ 3 | All grades | Grade ≥ 3 | All grades | Grade ≥ 3 |
| | Number of patients (%) | | | | | |
| Adverse effects | | | | | | |
| Fatigue | 10 (34) | 2 (7) | | | 6 (33) | |
| Appetite loss | 6 (21) | | 2 (8) | 1 (4) | 3 (17) | 1 (6) |
| Nausea | 5 (17) | | | | 3 (17) | |
| Hypertension | 2 (7) | | | | | |
| Taste disorder | 2 (7) | | | | 2 (11) | |
| Liver dysfunction | | | 1 (4) | | 1 (6) | |
| Hyponatremia | | | 1 (4) | 1 (4) | | |
| Diarrhea | | | 1 (4) | | | |
| Others | 1 (3) | | | | 2 (11) | |
| Workaround | | | | | | |
| Dose reduction | 14 (48) | | 2 (8) | | 12 (67) | |
| Interruption | | | 1 (4) | | | |
| Discontinuation | 1 (3) | | 2 (8) | | 1 (6) | |

enzalutamide was not changed in terms of PSA-PFS and TTF, regardless of flutamide use as shown in Fig. 3a, b. Furthermore, there was no difference in the OS after CRPC regardless of flutamide use.

From the result of this study, flutamide was demonstrated to be inferior to enzalutamide as first-line therapy for CRPC after CAB therapy; however, 46% of patients treated with flutamide had PSA response, indicating a decrease in PSA by ≥ 50% from baseline at 3 months, and 61.5% of patients had PSA decline from baseline. Moreover, the median PSA-PFS was 8.6 months. The previous studies on flutamide as AAT revealed that the responders, whose PSA decline was > 50% from baseline, had better prognosis and achieved sufficient benefits from flutamide [4, 5, 7, 8]. PSA nadir and duration of sensitivity to CAB therapy are predictors of the AAT response [9, 22]. Responders to flutamide in this study had statistically lower PSA nadir and longer time to PSA nadir at CAB therapy than did non-responders. Similarly, responders to enzalutamide had the same characteristics (data not shown).

In this study, enzalutamide was equally effective for the responders to flutamide, similar to the patients who were treated directly with enzalutamide. Even if the flutamide did not work for some of the patients, the disadvantage might be kept to a minimum by early administration of enzalutamide. The adverse effects of flutamide observed in this study include a small number of cases with diarrhea and liver dysfunction, which was similar to the adverse effects found in a previous report [18]. On the other hand, patients treated with enzalutamide had some adverse effects, such as fatigue and appetite loss, which were similar to those previously reported [14]. In this study, only two patients discontinued enzalutamide due to adverse effects, which could be attributed to the fact that we used the original questionnaire of adverse effects as patient-reported outcomes, and we noted the adverse effects early and could intervene by reducing the treatment dose (160 to 120 mg/day). In terms of cost, flutamide is cheaper than enzalutamide ($185 vs $2456 in Japan) and flutamide may be effective for more than 2 years in some patients; thus, there is a $54,500 difference in medical expenses between the two therapies.

Recently, some studies have reported the effect of abiraterone use, which was not changed to flutamide, for CRPC patients after CAB therapy [23, 24]. For enzalutamide, similar results are suggested in this study, which indicate that ART, such as enzalutamide and abiraterone, does not have cross-resistance with the first-generation anti-androgen, and flutamide may not shorten the OS of CRPC patients. Currently, the first-generation anti-androgens, such as bicalutamide and flutamide, are not recommended in the CRPC guidelines, but treatment options should be taken into consideration and need to be verified in a prospective study because of their low cost and low incidence of adverse effects.

Current treatment trend of prostate cancer is upfront treatment by strong agents. Docetaxel and abiraterone are now available as standard drugs for metastatic hormone-sensitive prostate cancer according to the result of CHARTTED, STAMPEDE, and LATITUDE studies [25–27]. Moreover, enzalutamide was more effective than bicalutamide in men with CRPC after ADT [20, 21]. However, in all these trials, there were some patients who were not treated according to the current standard of treatment (e.g.. in LATITUDE study, ART drugs were used as subsequent life-prolonging therapy

in only 27% of the patients in the placebo group after disease progression), and they did not compare the early group with the deferred group. As in this study, the long-term effect may not be significant despite the positive proximity effect because of the deferred administration of standard drugs and it seems to be significant for comparison, including subsequent life-prolonging therapy. According to the findings of this study, it is important to investigate who among the patients will benefit the most with flutamide before enzalutamide. Flutamide may have therapeutic and economic potential for some CRPC patients who had lower PSA nadir and longer time to PSA nadir at CAB therapy.

There are some limitations in this study. This is a small-sized, retrospective study conducted at a single center. Given that the drug selection was dependent on the doctors and patients, a selection bias may have existed. Moreover, the number of subjects was too small, and the observation periods were too short to draw conclusions about the effect of AAT. Currently, two prospective clinical studies comparing enzalutamide with flutamide for CRPC after CAB therapy are ongoing (NCT02346578 and NCT 02918968). We are expecting that the results of the prospective studies will confirm our findings.

## Conclusions

Enzalutamide is significantly superior to flutamide as the first-line therapy for CRPC after CAB therapy with bicalutamide. However, AAT with flutamide may be suitable for some CRPC patients. Moreover, there was no difference in the OS after CRPC regardless of flutamide use, if enzalutamide was used as a subsequent therapy.

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### Compliance with ethical standards

**Conflict of interest** Taro Iguchi, Sayaka Yasuda, and Tatsuya Nakatani received a research grant from Astellas Pharma Inc. and Bayer Yakuhin, Ltd.; Taro Iguchi received lecture fees from Astellas Pharma Inc., Bayer Yakuhin, Ltd. Janssen Pharmaceutical K.K., and Sanofi K.K.; Satoshi Tamada, Minoru Kato, Taiyo Otoshi, Kosuke Hamada, and Takeshi Yamasaki have no conflict of interest.

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