Enzalutamide versus flutamide for castration-resistant prostate cancer after combined androgen blockade therapy with bicalutamide: the OCUU-CRPC study

Taro Iguchi, Satoshi Tamada, Minoru Kato, Sayaka Yasuda,Yuichi Machida, Tetsuji Ohmachi, Keiichi Ishii, Hiroyuki Iwata, Shinji Yamamoto, Tomohiro Kanamaru, Kazuya Morimoto, Taro Hase, Koichiro Tashiro, Koji Harimoto, Takashi Deguchi, Takahisa Adachi, Katsuki Iwamoto, Yoshinori Takegaki & Tatsuya Nakatani

Iguchi, T., Tamada, S., Kato, M. et al. Enzalutamide versus flutamide for castration-resistant prostate cancer after combined androgen blockade therapy with bicalutamide: the OCUU-CRPC study. *International Journal of Clinical Oncology*. 25, 486–494 (2020).
Doi:10.1007/s10147-019-01554-3

Enzalutamide versus flutamide for castration-resistant prostate cancer after combined androgen blockade therapy with bicalutamide: The OCUU-CRPC study

Taro Iguchi[1,*], Satoshi Tamada[1], Minoru Kato[1], Sayaka Yasuda[1], Yuichi Machida[2], Tetsuji Ohmachi[3], Keiichi Ishii[4], Hiroyuki Iwata[5], Shinji Yamamoto[6], Tomohiro Kanamaru[7], Kazuya Morimoto[8], Taro Hase[9], Koichiro Tashiro[10], Koji Harimoto[11], Takashi Deguchi[12], Takahisa Adachi[13], Katsuki Iwamoto[14], Yoshinori Takegaki[15], Tatsuya Nakatani[1]

[1]Department of Urology, Osaka City University Graduate School of Medicine, Osaka, Japan

[2]Department of Urology, Yao Municipal Hospital, Yao, Japan

[3]Department of Urology, Bell-land General Hospital, Sakai, Japan

[4]Department of Urology, Osaka City General Hospital, Osaka, Japan

[5]Department of Urology, Itami City Hospital, Itami, Japan

[6]Department of Urology, Ikuwakai Memorial Hospital, Osaka, Japan

[7]Department of Urology, Yao Tokushukai General Hospital, Yao, Japan

[8]Department of Urology, Osaka General Hospital of West Japan Railway Company, Osaka, Japan

[9]Department of Urology, Suita Municipal Hospital, Suita, Japan

[10]Department of Urology, Meijibashi Hospital, Matsubara, Japan

[11]Department of Urology, Fuchu Hospital, Izumi, Japan

[12]Department of Urology, PL Hospital, Tondabayashi, Japan

[13]Department of Urology, Osaka City Juso Hospital, Osaka, Japan

[14]Department of Urology, Ishikiriseiki Hospital, Higashiosaka, Japan

[15]Department of Urology, Minamiosaka Hospital, Osaka, Japan

Running title: Enzalutamide versus flutamide for CRPC

***Correspondence:**

Taro Iguchi

Department of Urology, Osaka City University Graduate School of Medicine

1-4-3 Asahi-machi, Abeno-ku, Osaka, 545-8585, Japan

Phone: +81-6-6645-3857

Fax: +81-6-6647-4426

Email: taro@msic.med.osaka-cu.ac.jp

ABSTRACT

Background: Before the androgen target therapy era, flutamide was widely used for castration-resistant prostate cancer in Japan. Enzalutamide is currently the recommended treatment; however, the efficacy and safety of enzalutamide and flutamide after combined androgen blockade therapy with bicalutamide, has not been compared.

Methods: Patients with castration-resistant prostate cancer who received combined androgen blockade therapy with bicalutamide were randomly assigned to receive either enzalutamide or flutamide. The primary endpoint for efficacy was the 3-month prostate-specific antigen response rate. This trial is registered with ClinicalTrials.gov (NCT02346578) and the University hospital Medical Information Network (UMIN000016301)

Results: Overall, 103 patients were enrolled. The 3- (80.8% vs. 35.3%; p<0.001) and 6-month (73.1% vs. 31.4%; p<0.001) prostate-specific antigen response rates were higher in the enzalutamide than in the flutamide group. The 3-month disease progression rates (radiographic or prostate-specific antigen progression) were 6.4% and 38.8% in the enzalutamide and flutamide groups, respectively (hazard ratio [HR]: 0.16; 95% confidence interval [CI]: 0.05–0.47; p<0.001); the 6-month rates were 11.4% and 51.1%, respectively (HR: 0.22; 95% CI: 0.09–0.50; p<0.001). Enzalutamide provided superior prostate-specific antigen progression-free survival compared with flutamide (HR: 0.29; 95% CI: 0.15–0.54; p<0.001). Median time to prostate-specific antigen

progression-free survival was not reached and was 6.6 months in the enzalutamide and flutamide groups, respectively.

Conclusions: As an alternative anti-androgen therapy in patients with castration-resistant prostate cancer who fail bicalutamide-combined androgen blockade therapy, enzalutamide provides superior clinical outcomes compared with flutamide. Enzalutamide should be preferred over flutamide in these patients.

Keywords: castration-resistant prostate cancer; enzalutamide; flutamide; randomized controlled trial

INTRODUCTION

Although prostate cancer has previously been more common in Western than in Asian populations, its incidence and mortality has been increasing in Japan in recent years, owing to the aging population and the Westernization of diets [1-3]. Androgen deprivation therapy is the primary standard therapy for metastatic hormone-sensitive prostate cancer worldwide. However, despite its high cost, combined androgen blockade (CAB) therapy comprising bicalutamide and a luteinizing hormone-releasing hormone analog is generally used in Japan owing to excellent long-term outcomes [4,5]. Moreover, a recent propensity score matching analysis revealed that CAB prolongs progression free survival in patients with prostate cancer [6]. Patients often progress, however, to castration-resistant prostate cancer (CRPC). The Japanese clinical practice guidelines for prostate cancer, 2012 recommended alternative anti-androgen therapy (AAT) with flutamide after CAB therapy with bicalutamide (Bic-CAB) for CRPC with good response to initial Bic-CAB therapy. In a Japanese cohort, the response rate of AAT with flutamide, defined as a decrease of >50% from the baseline serum prostate-specific antigen (PSA) level, was 22% or 34% [7,8]. AAT response rate variability may result from variable pharmacological effects or point mutations in androgen receptor (AR) genes that confer drug resistance to bicalutamide and/or flutamide [9]. Although there is no evidence to support the fact that flutamide as AAT prolongs overall survival (OS), some efficacy has been observed in terms of the PSA response, [7,8] and

we have observed long-lasting positive effects of AAT with flutamide in clinical practice. Furthermore, responders to AAT with flutamide have shown high cancer-specific survival rates [8]. In contrast, enzalutamide was approved as a novel therapeutic agent for CRPC in the US, Europe, and Japan, in 2012, 2013, and 2014, respectively; it is now used widely. In addition to AR antagonism, enzalutamide suppresses androgen signaling through various mechanisms including the inhibition of coactivator binding, impairment of nuclear translocation, and inhibition of binding to target gene receptor binding sequences; it also induces apoptosis [10]. CRPC demonstrates AR overexpression and coactivator activation, non-AR dependent signaling reinforcement, AR gene mutations, and elevated intracellular androgen concentrations. Therefore, based on its mechanisms of action, it should promote tumor regression [11,12]. Enzalutamide, abiraterone, and docetaxel were listed as the first-choice drugs for CRPC in the Japanese clinical practice guideline for prostate cancer, 2016 [13]. Furthermore, although flutamide is still widely used after Bic-CAB in clinical practice, recommendations for its use as AAT have been removed from clinical guidelines.

In the previous PREVAIL and AFFIRM studies, which were randomized, placebo-controlled, double-blind phase III studies in pre- or post-docetaxel metastatic CRPC, enzalutamide significantly improved OS, radiographic progression-free survival (rPFS), and time to PSA progression [14,15]. Furthermore, in the TERRAIN and STRIVE studies, which were randomized,

placebo-controlled, double-blind phase II studies comparing enzalutamide to bicalutamide, enzalutamide significantly prolonged progression-free survival (PFS), rPFS, and time to PSA progression [16,17]. However, no previous studies have directly compared the efficacy of enzalutamide and flutamide in AAT. Therefore, this multi-center, prospective, randomized study aimed to compare the efficacy of flutamide as AAT with that of early-initiated enzalutamide, following Bic-CAB in patients with CRPC.

PATIENTS AND METHODS

Study Design

The OCUU-CRPC study was a phase II, investigator-initiated, multi-center, open-labeled, randomized clinical trial comparing enzalutamide with flutamide as AAT in patients with CRPC after Bic-CAB therapy. The study was approved by the ethics committees of all participating institutions, and was conducted according to the Declaration of Helsinki, the International Conference on Harmonisation - Good Clinical Practice, and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. All patients provided written informed consent. The OCUU-CRPC study is registered at ClinicalTrials.gov (NCT02346578) and with the University hospital Medical Information Network (UMIN000016301).

Study Participants

The study population comprised patients with CRPC, who were previously treated with Bic-CAB, had serum testosterone levels of <50 ng/dL (1.73 nmol/L), and had progressive disease after confirmation of anti-androgen withdrawal syndrome. Disease progression was either diagnosed radiologically based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or by PSA progression. PSA progression was defined as a consecutive increase in PSA levels estimated at least thrice at 1-week intervals, with a final level of ≥2 ng/mL [18]. Patients were

randomly assigned to the enzalutamide (160 mg/day, 4 × 40 mg capsules once daily) or the flutamide (375 mg/day, 125 mg tablets thrice daily) groups in a 1:1 ratio by dynamic allocation, based on the metastatic status (M0 or M1) M0 was defined as the absence of bone metastases on bone scans, and the absence of soft-tissue disease; M1 was defined as bone metastases on bone scans or soft-tissue metastasis, including nodal involvement above the aortic bifurcation. Treatment was continued until the patient met the criteria for changing or discontinuing treatment. Treatment was changed in the event of occurrence of adverse effects (AEs) causing difficulties in continuing medication, worsening of symptoms, disease progression on radiography based on RECIST (version 1.1), or PSA progression based on the Prostate Cancer Working Group 2 criteria, as follows: (1) PSA increase of ≥25% and an absolute increase of ≥2 ng/mL above the nadir, which is confirmed by a second value obtained 3 or more weeks later, in case of decline, or (2) a PSA increase of ≥25%, and an absolute increase of ≥2 ng/mL after 12 weeks in case of no decline from the baseline. Treatment was discontinued in cases of withdrawal of consent, death, transfer to another hospital, or at the investigator's discretion. If flutamide was discontinued, enzalutamide was considered to be the primary drug for subsequent treatment. Patients were followed up until September 2018, irrespective of their date of registration. The inclusion and exclusion criteria have been mentioned previously [19].

Study End Points

The primary endpoint was the 3-month PSA response rate (i.e. the proportion of patients whose PSA had decreased by ≥50% when measured at the third month from baseline). The secondary endpoints were: (1) 3-month disease progression rate, (2) 6-month PSA response rate, (3) 6-month disease progression rate, (4) PSA progression-free survival (PSA-PFS) calculated for the initial drug in each arm, and (5) AEs for safety. Patients who required switching to other treatments from initial enzalutamide therapy owing to disease progression within 6 months, were considered to be "non-responders" irrespective of the efficacy of subsequent treatment. In addition, in patients requiring switching from flutamide to enzalutamide, the PSA response rates were calculated to determine the efficacy of enzalutamide in this group.

Statistical Analysis

In previous studies, 75% and 35.4% of patients treated with enzalutamide and flutamide, respectively, showed a 50% decrease in PSA at 3 months from the initiation of treatment [14,8]. In the present study, the total number of patients required to confirm the superiority of enzalutamide over flutamide with a superiority margin of 5%, detection power of 90%, and one-sided significance of 0.025 was estimated to be 82, with 41 in each group. Therefore, a target of

100 total patients with 50 patients in each group was set, to make allowance for those leaving the study.

The full data set was used for the primary and secondary endpoints, and the safety analysis set was used for safety assessment. For the primary endpoint, we calculated the proportion of patients with a ≥ 50% decrease in PSA from baseline at 3 months in each group, as well as the difference between the groups with 95% confidence intervals (CI). The Mantel-Haenszel test was used for the analysis, using metastatic status (present/absent) at baseline as a stratification factor. Regarding the secondary endpoints, the proportion of patients with a ≥ 50% decrease in PSA from baseline at 6 months, and the rates for ≥ 50% decline in disease progression from baseline at 3 and 6 months, were calculated for each group. The intergroup differences in rates and 95% CIs were also calculated. The Mantel-Haenszel test was used for analysis, with metastatic status at baseline as a stratification factor. For PSA-PFS, a resurgence in PSA was treated as an event, and discontinuation or leaving the study for other reasons were treated as data cut-off points. If there was no resurgence in PSA by the end of the observation period, the level at the end of the observation period was treated as the cut-off. Survival rates by study group were estimated using the Kaplan-Meier method and were analyzed using the stratified log-rank test, using metastasis status at baseline as a stratification factor. Intergroup hazard ratios (HRs) and 95% CIs were also calculated. For the safety endpoint, we aggregated the frequency and prevalence of AEs or

adverse reactions occurring after baseline, by study group. All statistical analyses were performed using the SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) software package, and $P<0.05$ was considered statistically significant.

RESULTS

Patients and Treatment Duration

A total of 103 patients recruited from 15 institutions in Japan between February 6, 2015 and February 14, 2018, were randomized to either the enzalutamide group (n=52) or the flutamide group (n=51) by dynamic allocation, based on the metastatic status (M0, M1) (Figure 1). All patients received at least one dose of either study drug. The patient enrollment flow chart is shown in Figure 1. The baseline demographic and disease characteristics are shown in Table 1.

Efficacy

Primary endpoint

The 3-month PSA response rate was significantly higher in the enzalutamide group than in the flutamide group (80.8% vs. 35.3%; $p<0.001$). The mean percent change in PSA from baseline to 3 months was -83.2 and -6.1% in the enzalutamide and flutamide groups, respectively (Table 2, Figure 2).

Secondary endpoints

The 3-month disease progression rates in the enzalutamide and flutamide groups were 6.4% and 38.8%, respectively (HR: 0.16; 95% CI: 0.05–0.47; $p<0.001$), while the corresponding 6-month disease progression rates were 11.4% and 51.1%, respectively (HR: 0.22; 95% CI: 0.09–

0.50; p<0.001).

The 6-month PSA response rate was significantly higher in the enzalutamide than the flutamide group (73.1% vs. 31.4%; p<0.001; Table 2). The mean percentage maximum PSA decline from baseline in the entire observational period was -85.4% and -36.0% in the enzalutamide and flutamide groups, respectively (Figure 3). Enzalutamide was associated with significantly improved PSA-PFS compared with flutamide (HR: 0.29; 95% CI: 0.15–0.54; p<0.001). The median time to PSA-PFS was not reached and was 6.6 months in the enzalutamide and flutamide groups, respectively (Figure 4, Table 4).

Safety

The treatment-related AEs are summarized in Table 3. In total, 29 and 6 patients in the enzalutamide group and flutamide group, respectively, developed treatment-related AEs. Furthermore, AE-related treatment discontinuation was observed in 8 (decreased appetite: 4; anaphylactic reaction, seizure, QT prolongation, and rash: 1 each) and 6 patients (hepatic dysfunction and diarrhea: 2 each; breast pain and anorexia: 1 each) in the enzalutamide and flutamide groups, respectively. Meanwhile, AE-related dose reduction was required 21 and 4 patients in the enzalutamide and flutamide groups, respectively. As shown in Table 3, fatigue, decreased appetite, nausea, anemia, and dysgeusia were observed in at least 2% of patients in the

enzalutamide group; the corresponding AEs in the flutamide group included hepatic dysfunction, decreased appetite, anemia, and diarrhea. Grade ≥3 AEs occurred in 7 and 4 patients in the enzalutamide and flutamide groups, respectively; 1 patient in the enzalutamide group experienced a seizure, which was not severe and disappeared with discontinuation of the drug.

DISCUSSION

The OCUU-CRPC trial is the first randomized prospective trial to compare the efficacy and safety of AAT with flutamide vs. early-initiated enzalutamide therapy following Bic-CAB in patients with CRPC. At 3 months, the proportion of patients achieving ≥50% reductions in PSA was significantly greater in the enzalutamide than in the flutamide group. In terms of the distribution of PSA change rates at this time, the trend for maximum decline in PSA in the enzalutamide group (80.8%) was similar to that observed in the TERRAIN study at an equivalent point in time of 13 weeks. However, the trend for the flutamide group was similar to that of the bicalutamide group in the TERRAIN study [16]. At 6 months from baseline, the proportion of patients achieving ≥50% reductions in PSA and the maximum decline in PSA were also significantly higher in the enzalutamide than the flutamide group. The 3- and 6-month disease progression rates were also significantly lower in the enzalutamide than the flutamide group. Only 2 patients demonstrated radiographic progression before PSA progression (1 in each group). However, as the timing for imaging was not prescribed in the protocol, and was performed at the physicians' discretion, the exact number of patients with radiographic progression without PSA progression was unknown. Additionally, the median PSA-PFS was significantly longer in the enzalutamide than the flutamide group.

The above results indicate that AAT with early-initiated enzalutamide has superior efficacy

over flutamide in CRPC. Moreover, since the non-metastatic and metastatic numbers in the present study (33% and 67%, respectively) were similar to those of the STRIVE study (35% and 65%, respectively), we speculate that the present results confirm the efficacy and safety of enzalutamide and flutamide in patients with bicalutamide failure, as observed in the STRIVE study [17].

The safety profiles of the present study tended to be similar to those of the previous studies [20,15,14]. Anaphylactic reactions and seizures were observed in 1 patient each in the enzalutamide group. The former was severe, and was managed with steroid treatment and drug discontinuation; the latter disappeared with drug discontinuation, thereby demonstrating the safety of enzalutamide.

Flutamide is known to cause severe hepatic dysfunction [20]; in the present study, hepatic dysfunction of grade ≥3 occurred in 3 patients. However, since they recovered after treatment suspension or discontinuation, AAT with flutamide could be a feasible treatment option with regular hepatic function testing.

In the present study, the outcomes of CRPC were significantly superior in the enzalutamide than the flutamide group, in terms of the PSA response. However, owing to the challenges in treating enzalutamide- and taxane-resistant CRPC, other therapeutic strategies need to be established and validated before enzalutamide initiation [21].

In the present study, although the efficacy of flutamide was low, it was still effective in approximately 30% of patients. This finding was similar to that of previous studies on PSA response to AAT with flutamide, following Bic-CAB in Japanese patients [7,8,22,23]. Furthermore, in our previous, retrospective study comparing first- and second-line enzalutamide following flutamide in CRPC after Bic-CAB, the PSA levels decreased in all patients in the second-line enzalutamide group, and there were no significant differences in time to treatment failure of enzalutamide or OS between the two strategies [24]. Since AAT with flutamide prior to enzalutamide initiation is expected to confer economic benefits, future studies will need to establish evidence for the need of sequential therapy including flutamide. Additionally, the present study did not demonstrate a clear benefit of enzalutamide in terms of prolonged OS or cancer-specific survival, when AAT was effective. Therefore, these issues need to be resolved in a future follow-up of the present study.

In the OCUU-CRPC study, enzalutamide significantly decreased the risk of progression compared with flutamide in patients with CRPC after Bic-CAB therapy. This indicates that enzalutamide should be preferred over flutamide after CAB therapy in patients with CRPC. Further larger studies are needed to validate our findings.

ACKNOWLEDGEMENTS

The following individuals and institutions participated in the OCUU-CRPC study: T. Yamasaki, K. Kuratsukuri, N. Kuwabara, and T. Iwai of the Osaka City University, Osaka, Japan, C. Masuda, Y. Kuroki, and K. Oguma of the Fuchu Hospital, Izumi, Japan, Y. Yamakoshi of Ishikiriseiki Hospital, Higashi-Osaka, Japan, Y. Nita and K. Uemiya of the Itami Municipal Hospital, Itami, Japan, Y. Ohhara of Minamiosaka Hospital, Osaka, Japan, M. Yoshimoto and S. Sugita of Ohno Memorial Hospital, Osaka, Japan, W. Sakamoto of the Osaka City General Hospital, Osaka, Japan, C. Nishihara of the Osaka City Juso Hospital, Osaka, Japan, Y. Yoneda and Y. Komemushi of the Osaka General Hospital of West Japan Railway Company, Osaka, Japan, T. Ito and T. Sonoda of PL Hospital, Tondabayashi, Japan, M. Mitsuhashi of Shirasagi Hospital, Osaka, Japan, N. Kumada and J. Matsuda of Suita Municipal Hospital, Suita, Japan, S. Ikemoto and M. Kamizuru of the Yao Municipal Hospital, Yao, Japan, and H. Iimori and M. Kosoku of Yao Tokushukai General Hospital, Yao, Japan. We would like to thank Editage [http://www.editage.jp] for editing and reviewing this manuscript for English language.

CONFLICT OF INTEREST DISCLOSURE STATEMENT

This study was funded by Astellas Pharma Inc. Taro Iguchi has served as a consultant or advisor, has participated in the speakers' bureau, and has obtained research funding from Bayer, has served

as a consultant or advisor and has participated in the speakers' bureau for Janssen, and has served as a consultant or advisor, participated in the speakers' bureau, and has obtained research funding from Astellas, and has participated in the speakers' bureau of Sanofi. Sayaka Yasuda has received research funding from Astellas and Bayer. Tatsuya Nakatani has obtained research funding from Astellas and Bayer. The other authors declare that they have no competing interests. The funders had no role in the study design, collection of data, analyses, interpretation, or preparation of the manuscript.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I et al. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68 (6):394-424. doi:10.3322/caac.21492

2. Cancer statistics in Japan-2017. https://www.fpcr.or.jp/pdf/p21/cancer_statistics_2018.pdf. Accessed November 1 2018

3. Shin S, Saito E, Sawada N et al. (2018) Dietary patterns and prostate cancer risk in Japanese: the Japan Public Health Center-based Prospective Study (JPHC Study). Cancer Causes Control 29 (6):589-600. doi:10.1007/s10552-018-1030-3

4. Akaza H (2011) Combined androgen blockade for prostate cancer: review of efficacy, safety and cost-effectiveness. Cancer Sci 102 (1):51-56. doi:10.1111/j.1349-7006.2010.01774.x

5. Ueno S, Namiki M, Fukagai T et al. (2006) Efficacy of primary hormonal therapy for patients with localized and locally advanced prostate cancer: a retrospective multicenter study. Int J Urol 13 (12):1494-1500. doi:10.1111/j.1442-2042.2006.01604.x

6. Onozawa M, Akaza H, Hinotsu S et al. (2018) Combined androgen blockade achieved better oncological outcome in androgen deprivation therapy for prostate cancer: Analysis of community-based multi-institutional database across Japan using propensity score matching. Cancer Med 7 (10):4893-4902. doi:10.1002/cam4.1735

7. Miyake H, Hara I, Eto H (2005) Clinical outcome of maximum androgen blockade using flutamide as second-line hormonal therapy for hormone-refractory prostate cancer. BJU Int 96 (6):791-795. doi:10.1111/j.1464-410X.2005.05766.x

8. Suzuki H, Okihara K, Miyake H et al. (2008) Alternative nonsteroidal antiandrogen therapy for advanced prostate cancer that relapsed after initial maximum androgen blockade. J Urol 180 (3):921-927. doi:10.1016/j.juro.2008.05.045

9. Taplin ME, Bubley GJ, Shuster TD et al. (1995) Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. N Engl J Med 332 (21):1393-1398. doi:10.1056/NEJM199505253322101

10. Tran C, Ouk S, Clegg NJ et al. (2009) Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 324 (5928):787-790. doi:10.1126/science.1168175

11. Locke JA, Guns ES, Lubik AA et al. (2008) Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. Cancer Res 68 (15):6407-6415. doi:10.1158/0008-5472.CAN-07-5997

12. Montgomery RB, Mostaghel EA, Vessella R et al. (2008) Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res 68 (11):4447-4454. doi:10.1158/0008-5472.CAN-08-0249

13. Kakehi Y, Sugimoto M, Taoka R et al. (2017) Evidenced-based clinical practice guideline for prostate cancer (summary: Japanese Urological Association, 2016 edition). Int J Urol 24 (9):648-666. doi:10.1111/iju.13380

14. Beer TM, Armstrong AJ, Rathkopf DE et al. (2014) Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371 (5):424-433. doi:10.1056/NEJMoa1405095

15. Scher HI, Fizazi K, Saad F et al. (2012) Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367 (13):1187-1197. doi:10.1056/NEJMoa1207506

16. Shore ND, Chowdhury S, Villers A et al. (2016) Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. The Lancet Oncology 17 (2):153-163. doi:10.1016/s1470-2045(15)00518-5

17. Penson DF, Armstrong AJ, Concepcion R et al. (2016) Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. J Clin Oncol 34 (18):2098-2106. doi:10.1200/JCO.2015.64.9285

18. Scher HI, Halabi S, Tannock I et al. (2008) Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26 (7):1148-1159. doi:10.1200/JCO.2007.12.4487

19. Iguchi T, Tamada S, Kato M et al. (2019) Enzalutamide versus flutamide for castration-resistant prostate cancer after combined androgen blockade therapy with bicalutamide: study protocol for a multicenter randomized phase II trial (the OCUU-CRPC study). BMC Cancer 19 (1):339. doi:10.1186/s12885-019-5526-3

20. Eisenberger MA, Blumenstein BA, Crawford ED et al. (1998) Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 339 (15):1036-1042. doi:10.1056/nejm199810083391504

21. Shimizu Y, Tamada S, Kato M et al. (2018) Androgen Receptor Splice Variant 7 Drives the Growth of Castration Resistant Prostate Cancer without Being Involved in the Efficacy of Taxane Chemotherapy. J Clin Med 7 (11):444. doi:10.3390/jcm7110444

22. Fujikawa K, Matsui Y, Fukuzawa S et al. (2000) Prostate-specific antigen levels and clinical response to flutamide as the second hormone therapy for hormone-refractory prostate carcinoma. Eur Urol 37 (2):218-222. doi:10.1159/000020121

23. Yasui M, Uemura K, Yoneyama S et al. (2016) Predictors of poor response to secondary alternative antiandrogen therapy with flutamide in metastatic castration-resistant prostate cancer. Japanese journal of clinical oncology 46 (11):1042–1046. doi:10.1093/jjco/hyw110

24. Iguchi T, Tamada S, Kato M et al. (2019) Enzalutamide versus flutamide for castration-resistant prostate cancer after combined androgen blockade therapy with bicalutamide: a

retrospective study. Int J Clin Oncol 24 (7):848-856. doi:10.1007/s10147-019-01413-1

FIGURE LEGENDS

Figure 1. CONSORT diagram.

Figure 2. Percentage change in prostate-specific antigen (PSA) at 3 months from baseline, presented as a waterfall plot. Enzalutamide (red), flutamide (blue).

Figure 3. Maximum percentage prostate-specific antigen (PSA) change at 6 months from baseline, presented as a waterfall plot. Enzalutamide (red), flutamide (blue).

Figure 4. Kaplan-Meier curve of time to prostate-specific antigen (PSA) progression. Enzalutamide (red), flutamide (blue).

Abbreviations: IQR: interquartile range; CI: confidence interval; HR: hazard ratio; n: number; NE: not estimable.

Fig. 1 Patient enrollment flowchart

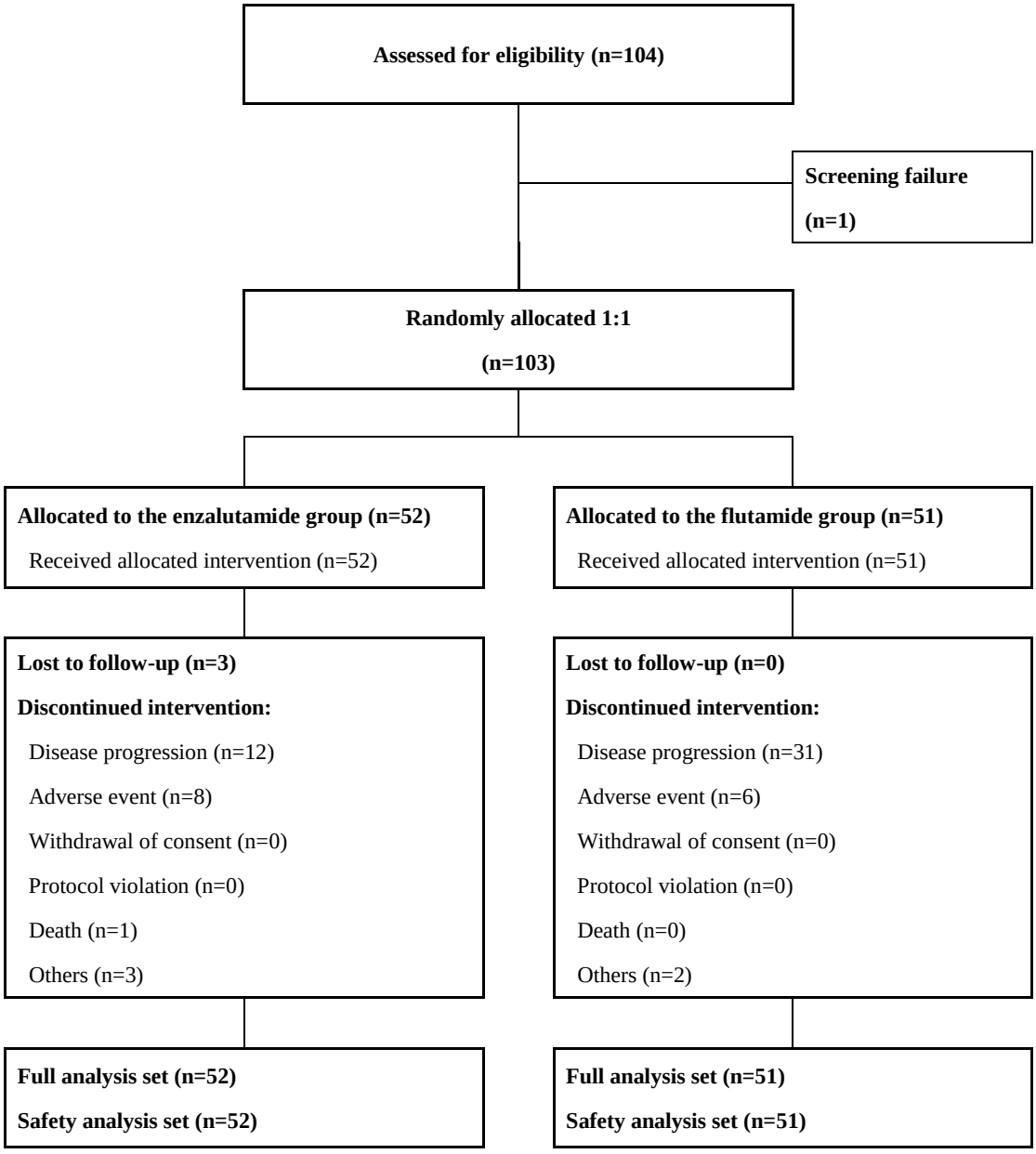

Fig. 2 The mean percent change in PSA from baseline to 3 months in the enzalutamide and flutamide groups

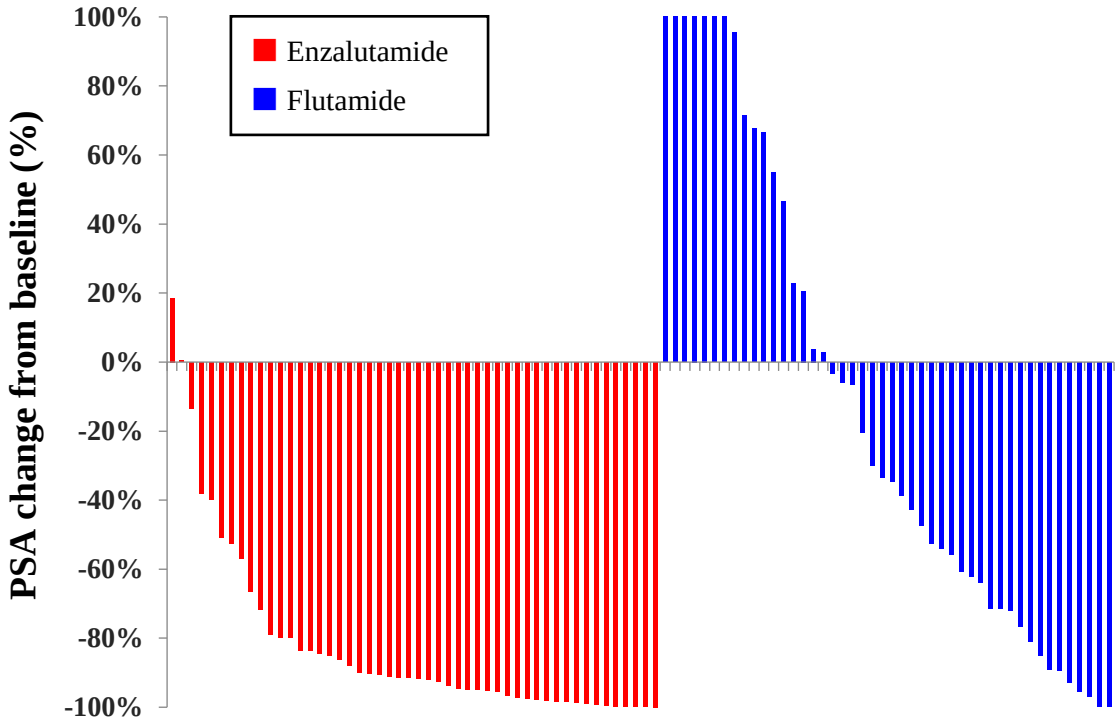

Fig. 3 The mean percentage maximum PSA decline from baseline in the enzalutamide and flutamide groups in the entire observational period

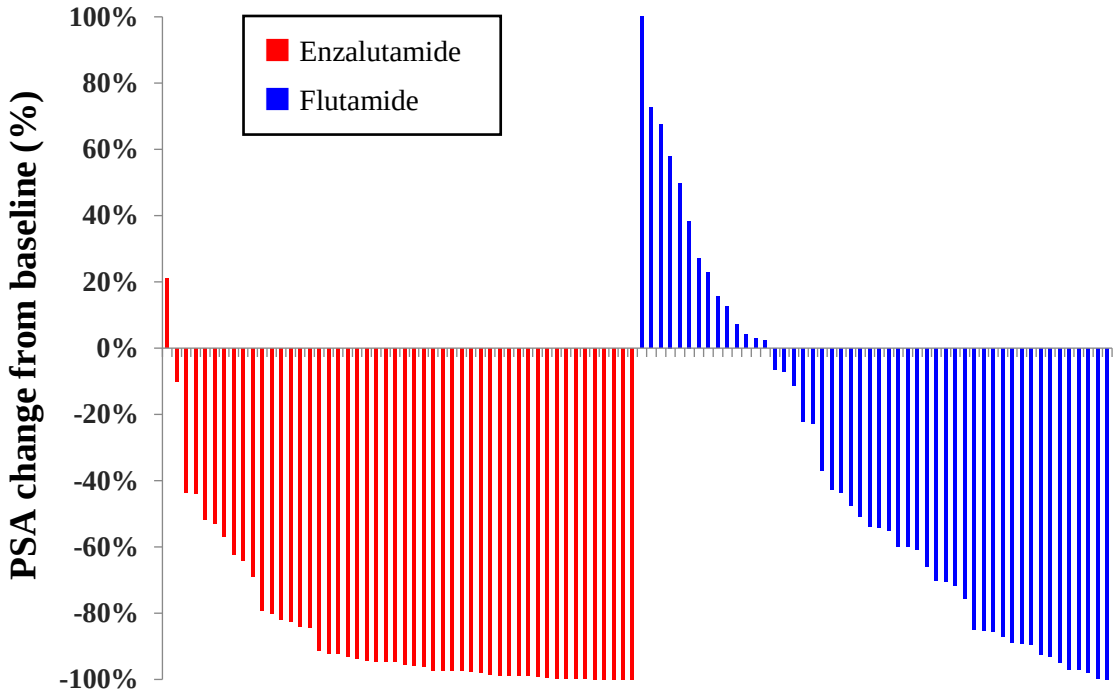

Fig. 4 The median time to PSA progression-free survival in the enzalutamide and flutamide groups

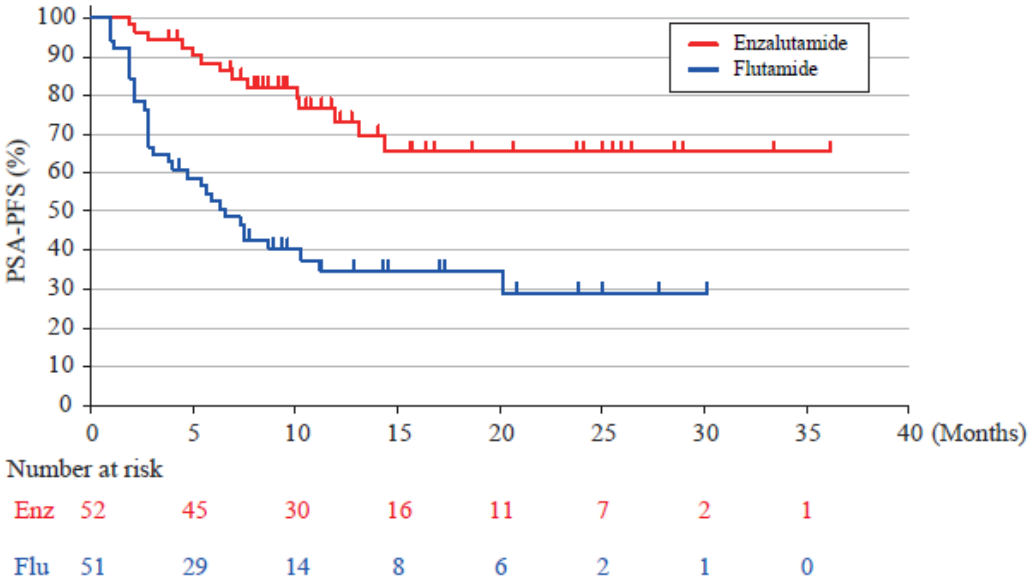

Table 1. Baseline demographic and disease characteristics

	Enzalutamide group (n=52)	Flutamide group (n=51)
Median age, years (range)	78 (61, 88)	77 (62, 91)
ECOG PS, n (%)		
0	30 (57.7)	41 (80.4)
1	22 (42.3)	10 (19.6)
Distant metastasis, n (%)		
M0	18 (34.6)	16 (31.4)
M1	32 (61.5)	33 (64.7)
Localization of metastasis, n (%)		
Bone	35 (67.3)	35 (68.6)
Lung	4 (7.7)	7 (13.7)
Liver	1 (1.9)	1 (2.0)
Others	0 (0.0)	1 (2.0)
Lymph node metastasis, n (%)		
N0	25 (48.1)	21 (41.2)
N1	24 (46.2)	29 (56.9)
Median PSA, μg/mL (range)	6.78 (2.01, 86.00)	5.62 (2.16, 330.20)
Median testosterone, ng/dL (range)	13.4 (0.1, 40.0)	13.0 (0.1, 47.0)
Median lactate dehydrogenase, U/L (range)	203 (113, 1136)	208 (88, 416)
Median alkaline phosphatase, U/L (range)	287 (116, 1144)	224 (96, 2630)
Median hemoglobin, g/dL (range)	13.1 (9.2, 16.4)	13.0 (8.3, 16.3)
Gleason score at initial diagnosis, n (%)		
≤7	5 (9.6)	5 (9.8)
8	18 (34.6)	13 (25.5)
9	16 (30.8)	21 (41.2)
10	7 (13.5)	6 (11.8)
Prior radical therapy, n (%)		
None	47 (90.4)	46 (90.2)
Prostatectomy	1 (1.9)	4 (7.8)
EBRT	4 (7.7)	1 (2.0)
AWS, n (%)		
Yes	8 (15.4)	13 (25.5)
No	44 (84.6)	38 (74.5)
Median time to CRPC, months (range)	19.3 (5.1, 145.1)	14.3 (5.1, 53.8)
Median duration of ADT, months (range)	15.8 (2.1, 145)	13.2 (4.1, 58.9)
FACT-P total score, median (range)	116.7	122.7

[a]ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: number; PSA: Prostate-specific antigen; EBRT: External beam radiation therapy; AWS: Anti-androgen withdrawal syndrome; CRPC: Castration-resistant prostate cancer; ADT: Androgen deprivation therapy; FACT-P: Functional assessment of cancer therapy-prostate.

Table 2. PSA response and disease progression rates

Characteristics	Enzalutamide group (n=52) n, (%)	Flutamide group (n=51) n, (%)	Rate difference, %, [95% CI]	*p*-value
PSA response rate at 3 months	42 (80.8)	18 (35.3)	45.1 [28.2, 62.0]	<0.001
PSA response rate at 6 months	38 (73.1)	16 (31.4)	41.1 [23.7, 58.5]	<0.001
Disease progression rate at 3 months	3/47 (6.4)	19/49 (38.8)	-31.9 [-47.0, -16.9]	<0.001
Disease progression rate at 6 months	5/44 (11.4)	24/47 (51.1)	-38.7 [-55.1, -22.3]	<0.001

[a]PSA, Prostate-specific antigen; n, number; CI, confidence interval

Table 3. Treatment-related adverse events

Event, n (%)		Enzalutamide group (n=52)		Flutamide group (n=51)	
AEs leading to treatment withdrawal		8 (15.4)		6 (11.8)	
AEs leading to dose reduction		21 (40.4)		4 (7.9)	
		All grade	**Grade 3≥**	**All grade**	**Grade 3≥**
AEs		**29 (55.8)**	**7 (13.5)**	**6 (11.8)**	**4 (7.9)**
	Fatigue	10 (19.3)	2 (3.8)	1 (2.0)	0
	Loss of appetite	8 (15.4)	2 (3.8)	3 (5.9)	1 (2.0)
	Nausea	6 (11.5)	0	0	0
	Liver dysfunction	1 (1.9)	1 (1.9)	5 (9.8)	3 (5.9)
	Anemia	3 (5.8)	0	3 (5.9)	0
	Diarrhea	1 (1.9)	0	2 (3.9)	0
	Taste dysgeusia	2 (3.8)	0	0	0
	Anaphylactic reaction	1 (1.9)	1 (1.9)	0	0
	Fall	1 (1.9)	1 (1.9)	0	0
	Seizure	1 (1.9)	0	0	0
	Thrombocytopenia	1 (1.9)	0	0	0
	Hypertension	1 (1.9)	0	0	0
	Ventricular arrhythmia	1 (1.9)	0	0	0
	Insomnia	1 (1.9)	0	0	0
	Skin drying	1 (1.9)	0	0	0
	Rash	1 (1.9)	0	0	0
	Mottled papule eruptions	1 (1.9)	0	0	0
	Prolonged QT *	1 (1.9)	-	0	0
	Breast pain	0	0	1 (2.0)	0

[a]n: number; AE: adverse event

*The grade of prolonged QT was unknown.

Table 4. Interquartile range of time to PSA progression

	Enzalutamide group (n=52)	Flutamide group (n=51)
IQR, Q1 (95% CI), months	11.93 (6.33, NE)	2.77 (1.90, 3.77)
Median (95% CI), months	NE (14.4, NE)	6.57 (3.07, 11.2)
IQR, Q3 (95% CI), months	NE (NE, NE)	NE (10.3, NE)
HR (95% CI)	**0.29 (0.15, 0.54)**	
p-value	**<0.001**	

IQR: interquartile range; CI: confidence interval;