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# Comparison of oncological outcomes of upfront androgen receptor signaling inhibitors and combined androgen blockade in Japanese patients with metastatic castration-sensitive prostate cancer

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**Abstract:** In recent years, randomized controlled trials have demonstrated that upfront androgen receptor signaling inhibitors (ARSIs) prolong overall survival (OS) compared with androgen deprivation therapy (ADT) alone or combined androgen blockade (CAB) in patients with metastatic castration-sensitive prostate cancer (mCSPC). However, it remains unclear whether upfront ARSI is superior to CAB in Asian populations, among which the efficacy of ADT/CAB is considered relatively high. In this study, we compared the oncological outcomes of upfront ARSI and CAB in Japanese patients with mCSPC. Patients with mCSPC who underwent systemic therapy between May 2009 and October 2023 were enrolled retrospectively. Propensity score matching (PSM) was performed to compare the castration-resistant prostate cancer-free survival (CRPC-FS), cancer-specific survival (CSS), and OS between patients treated with upfront ARSI (ARSI group) and those treated with CAB (CAB group). In total, 30 and 142 patients were enrolled in the ARSI and CAB groups, respectively. After PSM (25 patients in each group), CRPC-FS was significantly longer in the ARSI group than in the CAB group (median: 36.7 *vs.* 12.3 months, hazard ratio: 0.44, 95% confidence interval: 0.20–0.97, $p = 0.035$). No significant differences were observed in CSS or OS between the two groups. In conclusion, when compared to CAB, upfront ARSI might have the potential to extend CRPC-FS among individuals in the Japanese population.

***Keywords*:** castration-sensitive prostate cancer, androgen receptor signaling inhibitors, combined androgen blockade, castration-resistant prostate cancer-free survival, propensity score matching

## Introduction

Prostate cancer is a predominant oncological concern among men in Japan and worldwide. Although the incidence and mortality rates of prostate cancer in East Asian populations are reported to be less than half of those in Caucasian and African-American populations (*1*), Japan has witnessed a notable increase in prostate cancer cases, reaching 9,474 in 2019, more than double the number of 5,399 deaths recorded in 1995 (*2*). As life expectancy increases, more patients are being diagnosed with metastatic prostate cancer at the time of initial diagnosis. The standard treatment for patients with metastatic castration-sensitive prostate cancer (mCSPC) has been androgen deprivation therapy (ADT), either by medical or surgical castration. However, many patients develop castration-resistant prostate cancer (CPRC) and die several years after ADT initiation. Asian populations, including the Japanese, are generally more susceptible to ADT than Western populations (*3*). In Japan, combined androgen blockade (CAB) therapy using ADT in combination with anti-androgens has been used for the treatment of mCSPC since 2000. However, a phase III randomized controlled trial (RCT) comparing CAB with ADT alone showed that CAB prolonged overall survival (OS) compared with ADT alone for cT3-4 or cN1 prostate cancer, but showed no advantage for cM1 patients (*4*).

Recently, upfront treatment with androgen receptor signaling inhibitors (ARSIs), such as abiraterone (*5*), enzalutamide (*6*), and apalutamide (*7*), has been shown to prolong OS and progression-free survival (PFS) compared with ADT alone in several phase III RCTs and has become the standard treatment for mCSPC. As for RCTs comparing ARSI and CAB, ENZAMET trial showed that upfront enzalutamide prolonged OS and PFS compared with CAB, which is the combination of ADT and either bicalutamide, nilutamide, or flutamide (*8*). However, this trial did not enroll Japanese patients, and it is uncertain whether upfront ARSI will show superiority over CAB, even in Japanese patients for whom ADT/CAB is considered more effective than in

Western patients.

In this study, we retrospectively gathered data of Japanese patients with mCSPC and conducted a comparative analysis of efficacy of upfront ARSI and CAB using propensity score matching (PSM).

## Materials and Methods

### *Patients*

We conducted a retrospective study using the medical records of patients diagnosed with mCSPC and treated systemically at the Teikyo University Hospital between May 2009 and October 2023. The inclusion criteria consisted of patients newly diagnosed with prostate cancer and identified with metastasis through imaging studies, who underwent CAB or upfront ARSI. Exclusion criteria included patients who received treatments other than CAB or upfront ARSI, such as ADT alone or upfront docetaxel. A high/low volume of metastases was defined according to the CHAARTED criteria (*9*), and the extent of bone metastases was assessed using the extent of disease (EOD) score from bone scintigraphy. The criteria for defining CRPC included castrate levels of serum testosterone and evidence of disease progression, as indicated by imaging findings or elevation of prostate-specific antigen (PSA) levels. The determination of PSA worsening adhered to the definition provided by the Prostate Cancer Working Group 3 (*10*).

This study was approved by the Institutional Review Board of Teikyo University School of Medicine (no. 17-135-3), which waived the requirement for written informed consent due to the study's retrospective design. This study was conducted in compliance with the Declaration of Helsinki.

### *Treatment and assessment*

Treatment was continued until PSA worsening, radiographic progression, or clinical progression. CRPC-free survival (CRPC-FS), cancer-specific survival (CSS), and OS were defined as the time from the initiation of treatment to CRPC, prostate cancer mortality, and all-cause mortality, respectively.

### *Statistical analyses*

Differences in patient characteristics between the two groups were assessed using Student's *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. CRPC-FS, CSS, and OS were evaluated using Kaplan–Meier curves and the log-rank test, with statistically significant differences defined as $p$ value < 0.05. PSM was performed using the nearest-neighbor matching method with a caliper of 0.2, considering five covariates: initial PSA (iPSA), age, Eastern Cooperative Oncology Group performance status, grade group, and the CHAARTED criteria. Statistical analyses were performed using JMP Pro version 16.0.0.

## Results

### *Patient characteristics*

In total, 185 patients who underwent systemic treatment for mCSPC were enrolled in this study. Among them, we analyzed 30 patients who underwent upfront ARSI (ARSI group) and 142 patients who underwent CAB (CAB group) (Figure 1). Two patients who were initially treated with upfront docetaxel and 11 who received ADT alone were excluded from the analysis.

In the ARSI group, 14 patients received abiraterone (1,000 mg once daily), 11 received enzalutamide (160 mg once daily), and 5 received apalutamide (240 mg once daily), while all patients in the CAB group received bicalutamide (80 mg once daily). The clinicopathological characteristics of both the groups

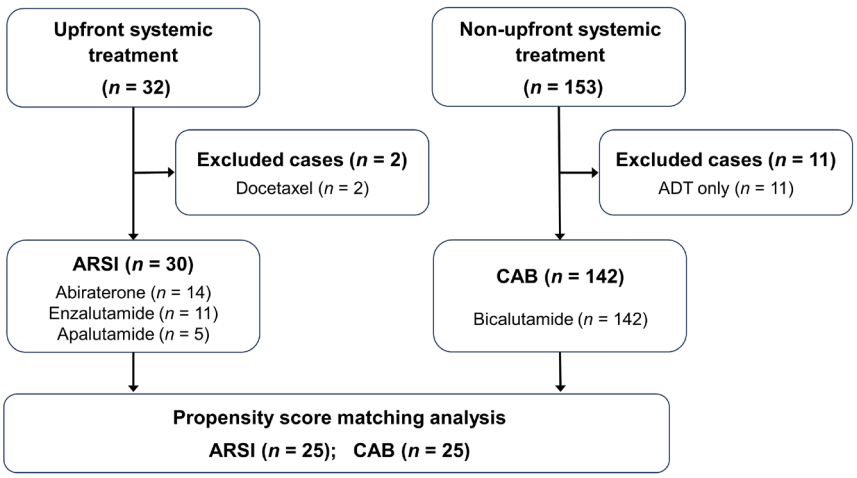


**Figure 1. Flow chart of patient selection among mCSPC patients.** mCSPC, metastatic castration-sensitive prostate cancer; ARSI, androgen receptor signaling inhibitor; CAB, combined androgen blockade.

are detailed in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=81*). The median follow-up period was 26.7 months (interquartile range [IQR]: 13.9–38.4 months) and 39.0 months (interquartile range: 22.1–68.1 months) in the ARSI and CAB groups, respectively.

*Comparison of prognostic outcomes before PSM*

Progression to CRPC occurred in 33% and 73% of patients in the ARSI and CAB groups, respectively, with a median CRPC-FS of 36.3 *vs*. 12.9 months (hazard ratio [HR]: 0.46, 95% confidence interval [CI]: 0.24–0.88, $p = 0.017$) (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=81*). Cancer-related death was observed in 13% and 43% of patients in the ARSI and CAB groups, respectively (median CSS: not reached *vs.* 71.6 months, HR: 0.65, 95% CI: 0.23–1.81, $p = 0.40$). Overall mortality rates were 23% and 58% in the ARSI and CAB groups, respectively, with median OS of 44.4 *vs.* 60.4 months (HR 0.81, 95% CI 0.37–1.79, $p = 0.60$). No adverse events of grade 3 or higher according to the Common Terminology Criteria for Adverse Events were reported in either group (data not shown).

*Comparison of prognostic outcomes after PSM*

Twenty-five patients in each group were matched using PSM. There were no significant differences in clinicopathological characteristics between the two groups after PSM (Table 1). In the matched cohorts, 36% and 88% of patients in the ARSI and CAB groups, respectively, progressed to CRPC, with median CRPC-FS of 36.7 *vs*. 12.3 months (HR: 0.44, 95% CI: 0.20–0.97, $p = 0.033$; Figure 2). Cancer-related death rates were 16% and 36% in the ARSI and CAB groups, respectively, with median CSS of 44.3 months *vs*. not reached (HR: 0.98, 95% CI: 0.28–3.44, $p = 0.98$). Overall mortality rates were 28% and 48% in the ARSI and CAB groups, respectively, with median OS of 44.3 *vs*. 78.7 months (HR: 1.59, 95% CI: 0.56–4.53, $p = 0.38$). Thus, although CSS and OS did not differ significantly between the two groups, CRPC-FS was significantly prolonged in the ARSI group.

## Discussion

The results of this study indicate that upfront treatment with ARSI for mCSPC may be more beneficial than treatment with CAB in Japanese patients. Although no significant differences were observed in CSS or OS, the CRPC-FS was significantly longer in the ARSI group than in the CAB group. Furthermore, no severe adverse events were recorded in either treatment group, suggesting that upfront ARSI treatment was well tolerated.

Japanese patients respond better to ADT than patients of the Western populations. A retrospective study comparing prostate cancer mortality rates between Japanese and American patients receiving ADT as

**Table 1. Baseline clinicopathological characteristics after PSM**

| Parameter | ARSI group ($n = 25$) | CAB group ($n = 25$) | $p$ value |
|---|---|---|---|
| Age, years, median (range) | 74 (55–86) | 76 (62–84) | 0.55[a] |
| Initial PSA, ng/mL, median (IQR) | 420 (39–2683) | 458 (65–3541) | 0.29[a] |
| Hemoglobin, g/dL, median (IQR) | 12.9 (11.3–14.0) | 12.8 (11.0–13.5) | 0.71[a] |
| ALP, IU/ml, median (IQR) | 153 (80–294) | 187 (94–399) | 0.98[a] |
| LD, IU/L, median (IQR) | 198 (177–291) | 211 (178–339) | 0.50[a] |
| ECOG PS, *n* (%) | | | |
| 0 | 14 (56) | 9 (36) | 0.35[b] |
| 1 | 10 (40) | 14 (56) | |
| ≥ 2 | 1 (4) | 2 (8) | |
| Grade group, *n* (%) | | | |
| ≤ 3 | 1 (4) | 2 (8) | 1.00[c] |
| ≥ 4 | 24 (96) | 23 (92) | |
| Metastatic site, *n* (%) | | | |
| Lymph node | 18 (72) | 17 (68) | 1.00[c] |
| Bone | 19 (76) | 23 (92) | 0.25[c] |
| Lung | 8 (32) | 4 (16) | 0.32[c] |
| CHAARTED criteria, *n* (%) | | | |
| Low volume | 7 (28) | 8 (32) | 1.00[c] |
| High volume | 18 (72) | 17 (68) | |
| EOD score, *n* (%) | | | |
| 0 | 6 (24) | 8 (32) | 0.77[b] |
| 1 | 3 (12) | 2 (8) | |
| ≥ 2 | 16 (64) | 15 (60) | |

[a]Student's *t*-test; [b]Chi-squared test; [c]Fisher's exact test. PSM, propensity score matching; ARSI, androgen receptor signaling inhibitors; CAB, combined androgen blockade; PSA, prostate-specific antigen; IQR, interquartile range; ALP, alkaline phosphatase; LD, lactate dehydrogenase; ECOG-PS, Eastern Cooperative Oncology Group performance status.

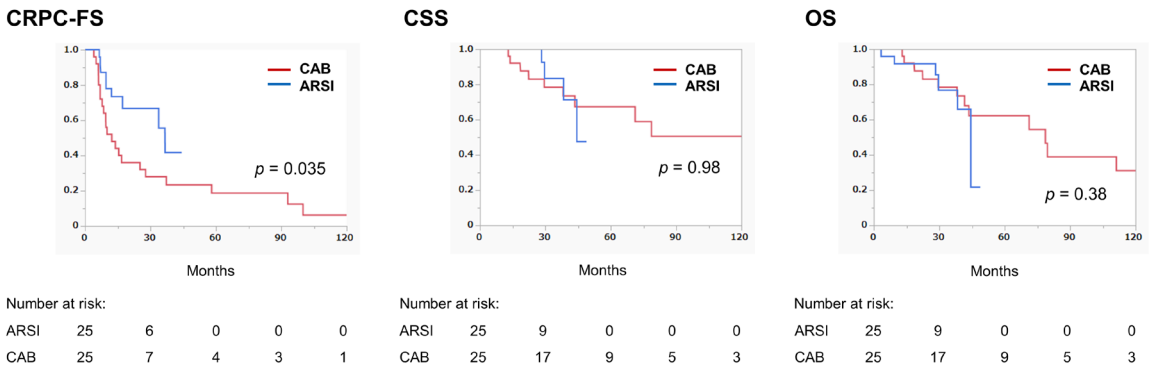


**Figure 2. Comparisons of CRPC-FS, CSS, and OS between the ARSI and CAB groups (*n* = 25 each) after PSM.** CRPC-FS, castration-resistant prostate cancer-free survival; CSS, cancer-specific survival; OS, overall survival; ARSI, androgen receptor signaling inhibitor; CAB, combined androgen blockade; PSM, propensity score matching.

primary therapy revealed that prostate cancer mortality in the Japanese patients was significantly lower than in the American patients, with a hazard ratio of 0.52 (*3*). Genetic disparities between races and differences in lifestyle factors such as diet may contribute to these variations. In addition, a multicenter retrospective analysis of Japanese patients showed that CAB treatment was more effective than ADT in prolonging PFS (*11*). Therefore, some opinions suggest that CAB is a sufficient treatment option, and that upfront treatment may not be necessary for mCSPC in Japanese patients.

Although no RCTs that compared upfront ARSI and CAB therapies in Japanese patients with mCSPC have been conducted, several retrospective studies have been reported (*12-16*). Ueda *et al. c*ompared matched cohorts of 28 patients each who received upfront abiraterone and CAB therapy, respectively, using PSM, demonstrating the superiority of upfront abiraterone in terms of OS and PFS (*12*). Similarly, Matsumura *et al.* compared matched cohorts of 63 patients each, who received upfront abiraterone and CAB therapy, respectively, using PSM and showed the superiority of upfront abiraterone in terms of OS and PFS (*13*). Conversely, Naiki *et al.* compared matched cohorts of 71 patients each, who received upfront abiraterone and CAB therapy, using PSM, finding upfront abiraterone to be superior in terms of PFS but not in terms of OS (*14*). Our results demonstrated the superiority of upfront ARSI over CAB in terms of CRPC-FS, but no superiority was observed in terms of CSS or OS, similar to the findings of Naiki *et al.* Recently, the J-ROCK Study, a large Japanese observational study comprising 974 patients, reported that upfront ARSI or docetaxel was superior to ADT or CAB in terms of PFS, CRPC-FS, and OS (*15,16*). Further validation in larger studies with longer follow-up periods is warranted to confirm the superiority of upfront ARSI over CAB in terms of CSS and OS in Japanese patients.

The present study has several limitations. First, the sample size was small and the follow-up duration was relatively short. These factors may have contributed to the lack of significant differences in CSS and OS. Second, this study was retrospective in nature. Despite performing PSM and matching to balance background factors, the reliability was inferior to that of an RCT.

In conclusion, based on our study utilizing PSM, there is an indication that upfront ARSI treatment may potentially extend CRPC-FS when compared with CAB in Japanese patients with mCSPC. Future efforts should involve accruing larger patient cohorts to further delineate the comparative efficacy of upfront ARSI and CAB therapies on CSS and OS.

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*Conflict of Interest*: The authors have no conflicts of interest to disclose.

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