Upfront Androgen Receptor-Axis-Targeted Therapies in Men with De Novo High-Volume Metastatic Hormone-Sensitive Prostate Cancer

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Purpose: The extent of effectiveness of upfront androgen receptor-axis-targeted therapies (ARAT) versus total androgen blockade (TAB) in improving prostate cancer-specific survival (CSS) and progression-free survival (PFS) in a real-world sample of Japanese patients with high-volume mHSPC remains unclear. We, therefore, investigated the efficacy and safety of upfront ARAT versus bicalutamide for de novo high-volume mHSPC in Japanese patients.

Material and Methods: This was a multicenter retrospective study that analyzed CSS, clinical PFS, and adverse events (AEs) in 170 patients with newly diagnosed high-volume mHSPC. Fifty-six patients were treated with upfront ARAT, and 114 of them were prescribed bicalutamide in addition to ADT between January 2018 and March 2021. The primary and secondary endpoints were CSS and PFS, respectively. A 1:1 nearest neighbor propensity score matching (PSM) with a caliper of 0.2 was performed to match the ARAT group to TAB patients.

Results: During the follow-up for a median of 21.5 months, the median CSS was not reached and 37 months in the upfront ARAT and total androgen blockade (TAB) groups, respectively (log-rank test: $P = 0.006$) by propensity score matching (PSM). Moreover, while the PFS of ARAT was unreached, the median PFS of TAB was 9 months (log-rank test: $P < 0.001$). Nine patients discontinued ARAT owing to grade $\geq$ 3 AEs; one patient who was treated with TAB had a grade 3 AE.

Conclusion: Upfront ARAT significantly prolonged the CSS and PFS of patients with high-volume mHSPC better than TAB, although ARAT was associated with a higher rate of grade $\geq$ 3 AEs. Upfront ARAT can be more beneficial for patients with de novo high-volume mHSPC than TAB.

Keywords: Upfront ARAT; bicalutamide; metastatic; hormone-sensitive; prostate cancer

INTRODUCTION

Prostate cancer has the highest incidence among male individuals in Japan and globally. The number of patients with this cancer was 1.44 million in 2016 worldwide and 78,400 in Japan in 2018.[1,2] Although the incidence of prostate cancer is relatively lower in the Middle East and Asia compared to Europe and the United States, prostate cancer caused 12,250 deaths in Japanese male individuals, and it ranks sixth among all male cancers in 2018.[3] Total androgen blockade (TAB) therapy, also known as combined androgen blockade (CAB) therapy, mainly androgen deprivation therapy (ADT) plus non-steroidal antiandrogens, such as bicalutamide, has been frequently used for the initial care of patients with metastatic hormone-sensitive prostate cancer (mHSPC) in Japan.

In recent years, docetaxel, abiraterone, enzalutamide, and apalutamide have been used in standard care for initial treatments for mHSPC instead of TAB or ADT alone, owing to the results of the CHAARTED, LATITUDE, ENZAMET/ARCHES, and TITAN trials.[4–8] The LATITUDE trial showed that abiraterone, a CYP17 inhibitor, with prednisone plus ADT substantially favored overall survival (OS) and radiographic progression-free survival (PFS) in newly diagnosed high-risk mHSPC patients when compared with ADT plus placebo treatment. High risk was defined as matching at least two of the following three criteria: Gleason score of $\geq$ 8, three or more bone metastatic lesions, and visceral metastasis. By contrast, high volume was defined as the presence of visceral metastases or at least four bone lesions, with one or more lesions present beyond the vertebral bodies and pelvis, based on the

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Received August 2022 & Accepted March 2023

Table 1. Patient demographics

Variables[a]	ARAT (N = 56)	TAB (N = 114)	*P*-value
Median (range) age (years)	72 (52-85)	77 (58-96)	< .001
Median (range) initial PSA (ng/mL)	286 (0.94-15,450)	473 (2.79-12,802)	.027
Median (range) pretreatment ALP (IU/L)	408.5 (67-21,104)	584 (56-11,600)	.419
Median (range) pretreatment Hb (IU/L)	13.3 (6.2-16.3)	12.1 (5.4-17.2)	.020
Median (range) pretreatment LDH (IU/L)	201 (125-503)	215 (106-864)	.073
Median (range) pretreatment BSI	3.77 (0-24)	3.35 (0-13.22)	.297
Median (range) pretreatment ECOG PS	0 (0-3)	1 (0-3)	.099
Median (range) pretreatment CCI	3 (1-6)	4 (1-7)	.005
Gleason score (n, %)			
6	0 (0%)	1 (0.9%)	.066
7	2 (3.6%)	1 (0.9%)	
8	5 (8.9%)	28 (24.6%)	
9	35 (62.5%)	25 (21.9%)	
10	9 (16.1%)	16 (14.0%)	
Missing data	5 (8.9%)	43 (37.7%)	
Visceral metastasis (n, %)	18 (32.1%)	17 (14.9%)	.009
Nadir PSA ≤ 0.2ng/mL in 3 months (n,%)	20 (35.7%)	14 (12.3%)	< .001

Investigations were from multiple municipal or private hospitals in Japan between January 2018 and March 2021.
Abbreviations: ARAT, androgen receptor-axis–targeted therapy; CCI, Charlson comorbidity index; PSA, prostate-specific antigen; TAB, Total Androgen Blockade
[a] Continuous variables were compared by independent samples t-test

CHAARTED trial results.[9] One of the main differences between high-risk and high-volume criteria is that high-risk criteria require a Gleason score. In this study, we adopted high-volume because some patients with mHSPC needed immediate therapies skipping prostate biopsies; current RCTs use high-volume criteria more commonly. The reports of the efficacy and safety of upfront androgen receptor-axis-targeted therapy (ARAT) in real-world Japanese high-volume mHSPC patients over the TAB group were few and remain unclear.[10,11]

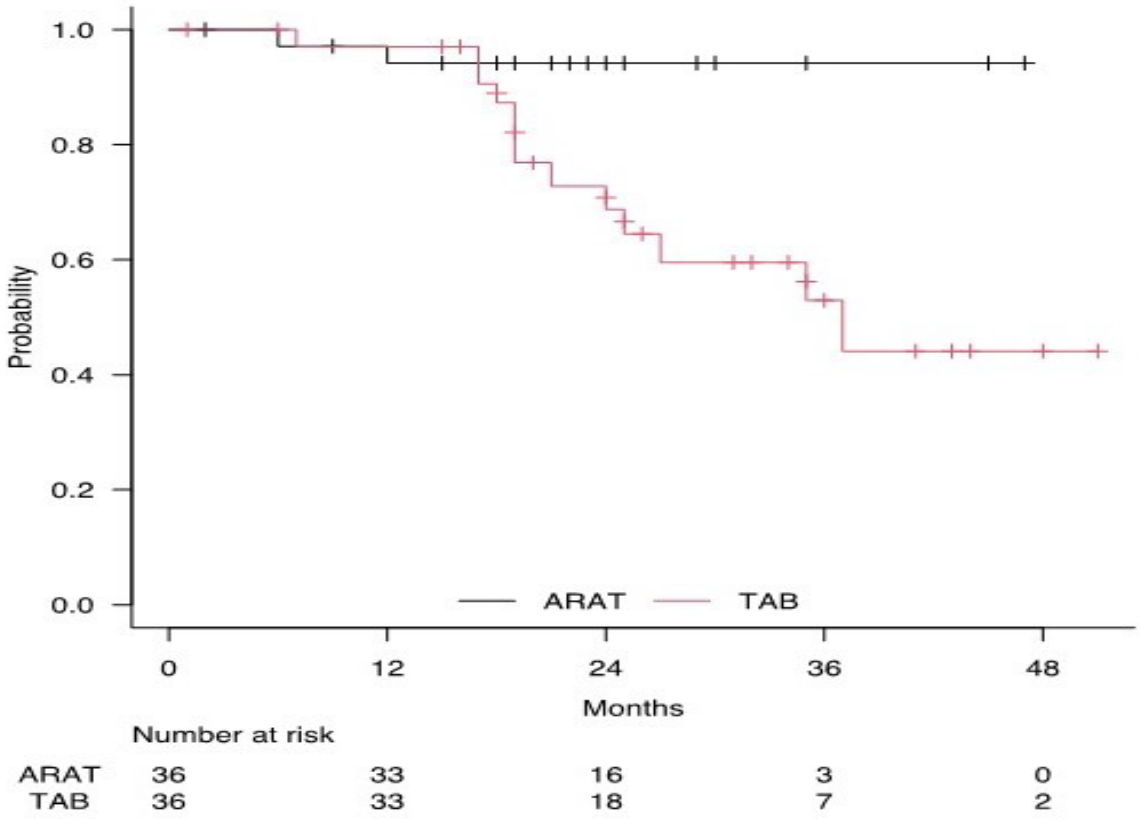

Figure 1. Kaplan-Meier estimates of cancer-specific survival in the ARAT and TAB groups. ARAT includes abiratetone, enzalutamide, and apalutamide. The median CSS was not achieved and was 37 months in the ARAT and TAB groups, respectively. There were two and 13 deaths in the ARAT and TAB groups, respectively. After PSM, the log-rank test was set at $P = .006$
Abbreviations: ARAT, androgen receptor-axis-targeted therapy (including abiraterone, enzalutamide, and apalutamide); TAB, total androgen blockade; CSS, cancer-specific survival; TAB, total androgen blockade

Table 2. Patient demographics after PSM

Variables[a]	ARAT (N = 36)	TAB (N = 36)	*P*-value
Median (range) age (years)	73 (64-85)	71.5 (60-89)	.498
Median (range) initial PSA (ng/mL)	359 (5.41-15,450)	324 (2.79-5,656)	.928
Median (range) pretreatment ALP (IU/L)	463 (105-21,104)	372 (100-4,455)	.692
Median (range) pretreatment Hb (IU/L)	13.2 (6.2-16.1)	13.0 (8.5-16.3)	.848
Median (range) pretreatment LDH (IU/L)	197 (125-503)	200 (106-605)	.710
Median (range) pretreatment BSI	5.35 (0-24)	1.98 (0-12.15)	.126
Median (range) pretreatment ECOG PS	0 (0-3)	0 (0-3)	.746
Median (range) pretreatment CCI	3 (2-6)	3 (2-5)	.328
Gleason score (n, %)			
6	0 (0%)	0 (0%)	.354
7	1 (2.8%)	1 (2.8%)	
8	4 (11.1%)	12 (33.3%)	
9	26 (72.2%)	15 (41.7%)	
10	5 (13.9%)	8 (22.2%)	
Visceral metastasis (n, %)	8 (22.2%)	6 (16.7%)	.554

Abbreviations: PSM, propensity score matching; ARAT, androgen receptor-axis–targeted therapy; CCI, Charlson comorbidity index; PSA, prostate-specific antigen; TAB, Total Androgen Blockade

[a] Continuous variables were compared by independent samples t-test

Therefore, we aimed to determine the efficacy and safety of upfront ARAT versus TAB in Japanese patients with de novo high-volume mHSPC. Propensity score matching (PSM) was addressed if biases exist between those two groups.

MATERIALS AND METHODS

Trial Design

This study retrospectively investigated the prostate cancer-specific survival (CSS) and PFS of patients with high-volume mHSPC treated with upfront ARAT or TAB in multiple municipal or private hospitals in Japan. Eligible patients were required to be at least 20 years old with newly diagnosed with high-volume mHSPC with 3 months or less ADT between January 2018 and March 2021. The definition of high-volume is the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis. The amount (%) of bone metastasis on bone scintigraphy is calculated as a bone scan index (BSI). Patients with Small cell prostate cancers were excluded. Patients were also excluded if they received any previous chemotherapy, radiation therapy, or surgery for metastatic prostate cancer. The primary and secondary endpoints were CSS and PFS, respectively. The CSS in this study was defined as the duration from the initial treatment to death from prostate cancer. PFS was defined as the duration from the initial treatment to the diagnosis of castration-resistant prostate cancer (CRPC). CRPC diagnosis was made based on European Association of Urology guidelines for prostate cancer. The guideline defines CRPC if one of the two criteria are met: (i) biochemical progression, which means that three consecutive increases in prostate-specific antigen (PSA) levels at least one week apart, resulting in two 50% increases over nadir, and a PSA level of >2 ng/mL, with a castrate serum testosterone level of less than 50 ng/dL or 1.7 nmol/L, or (ii) radiological progression, i.e., the appearance of two or more new bone lesions on bone scintigraphy or a soft tissue lesion according to the Response Evaluation Criteria in Solid Tumors criteria.[12] This study also assessed whether CSS in both groups was affected by nadir PSA, which achieved $\leq$ 0.2 ng/mL in 3 months since the start of initial treatment. The CSS in the study was defined as the duration from the initial treatment to death from prostate cancer.

The ethics committee of all the facilities approved this study, which was conducted in compliance with the Declaration of Helsinki. The ethics committees waived individual written informed consent because of the retrospective nature of this study, and Opt-out information was provided to patients on the website of Asahi General Hospital.

Table 3. Patient demographics in the TAB group

Variables[a]	Nadir PSA > 0.2 ng/mL (N = 100)	Nadir PSA ≤ 0.2 ng/mL (N = 14)	*P*-value
Median (range) age (years)	77 (58-96)	75 (63-89)	.959
Median (range) initial PSA (ng/mL)	592.5 (2.79-12,802)	277.0 (6.1-12,045)	.049
Median (range) pretreatment ALP (IU/L)	639.5 (56-11,600)	248 (75-4,349)	.072
Median (range) pretreatment Hb (IU/L)	11.8 (5.4-17.2)	14.0 (8.4-15.4)	.014
Median (range) pretreatment LDH (IU/L)	226.5 (106-864)	197 (139-279)	.182
Median (range) pretreatment BSI	4.41 (0-13.22)	0.56 (0-7.02)	.018
Median (range) pretreatment ECOG PS	1 (0-3)	0 (0-2)	.139
Median (range) pretreatment CCI	4 (0-7)	4 (2-6)	.407
Gleasen score (n, %)			
6	1 (1.1%)	0 (0%)	.019
7	0 (0%)	0 (0%)	
8	17 (18.1%)	11 (55.0%)	
9	24 (25.5%)	1 (5.0%)	
10	14 (14.9%)	2 (10.0%)	
Missing data	38 (40.4%)	6 (30.0%)	
Visceral metastasis (n, %)	12 (12.0%)	5 (35.7%)	.020

Abbreviations: ARAT, androgen receptor-axis–targeted therapy; CCI, Charlson comorbidity index; PSA, prostate-specific antigen; TAB, Total Androgen Blockade

[a] Continuous variables were compared by independent samples *t*-test

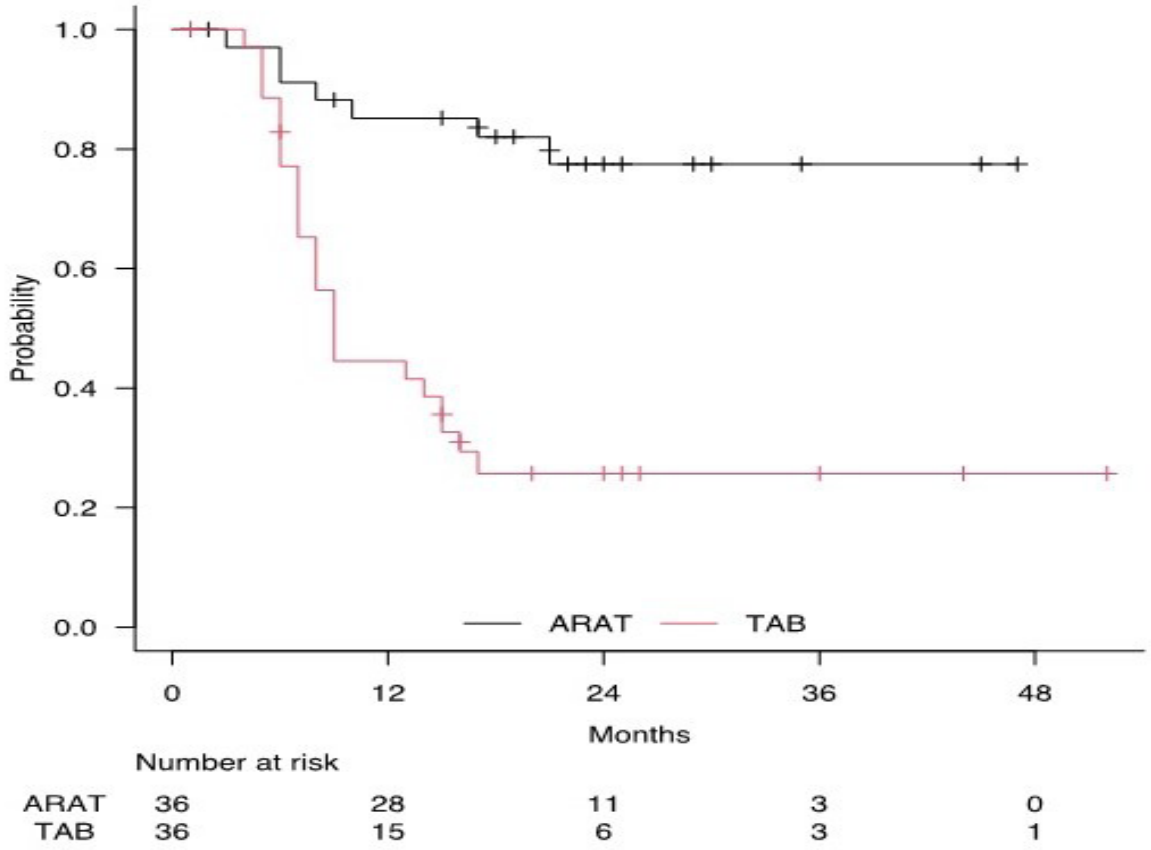

Figure 2. Kaplan-Meier estimates of PFS in the ARAT and TAB groups. The median PFS was not achieved in the ARAT group but was 9 months in the bicalutamide group. Eleven and 86 men developed CRPC in the ARAT and TAB groups, respectively. After PSM, the log-rank test was set at $P < .001$.
Abbreviations: ARAT, androgen receptor-axis–targeted therapy (including abiraterone, enzalutamide, and apalutamide); TAB, total androgen blockade; CRPC, castration-resistant prostate cancer; PFS, progression-free survival

Patients and Treatments

Men who were newly diagnosed with high-volume mHSPC between January 2018 and March 2021 in our hospital and other facilities participated in this study. The clinical cutoff date was March 2022. The median follow-up duration was 21.5 months. In this study, the ARAT group included patients newly diagnosed with high-volume mHSPC who were treated with abiraterone, enzalutamide, and apalutamide. Bone and visceral metastases were assessed using bone scintigraphy and computed tomography, respectively. Treatment was discontinued due to the occurrence of grade ≥ 3 adverse events (AEs) or due to the diagnosis of CRPC.

Statistical Analysis

EZR statistical software (Jichi Medical University Saitama Medical Center, Saitama, Japan) was used for all statistical analyses. The two groups were compared using the chi-square test. CSS and PFS were analyzed using the Kaplan-Meier method and log-rank test, and the statistical significance was set at $P < .05$. The Cox proportional hazards model was used for multivariate analysis, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The covariates included in the Cox model were treated as continuous values as shown in every relevant table. The safety profile of these drugs was assessed in patients who received at least one dose. A 1:1 nearest neighbor propensity score matching (PSM) with a caliper of 0.2 was performed to match the initial PSA and Gleason scores of the ARAT group to TAB patients.

The ethics committee of all the facilities approved this study, which was conducted in compliance with the Declaration of Helsinki. The ethical IRB number is 2022011801.

RESULTS

Patient Characteristics

A total of 170 men were newly diagnosed with high-volume mHSPC at multiple facilities between January 2018 and March 2021. Fifty-six of the 170 patients were treated with ARAT (39 with abiraterone [1000 mg/day] plus prednisolone [5 mg/day], 14 patients treated with enzalutamide [160 mg/day], 3 patients treated with apalutamide [240 mg/day]), and 114 patients were treated with bicalutamide (80 mg/day). The baseline demographics of patients and disease characteristics in both groups are shown in **Table 1** and were well balanced except for the significant differences in age, baseline Hb level, CCI, and presence or absence of visceral metastases.

Prostate CSS

During a median follow-up of 21.5 months, 5 of 56 patients in the ARAT group and 44 of 114 patients in the TAB group died of prostate cancer. One-to-one PSM

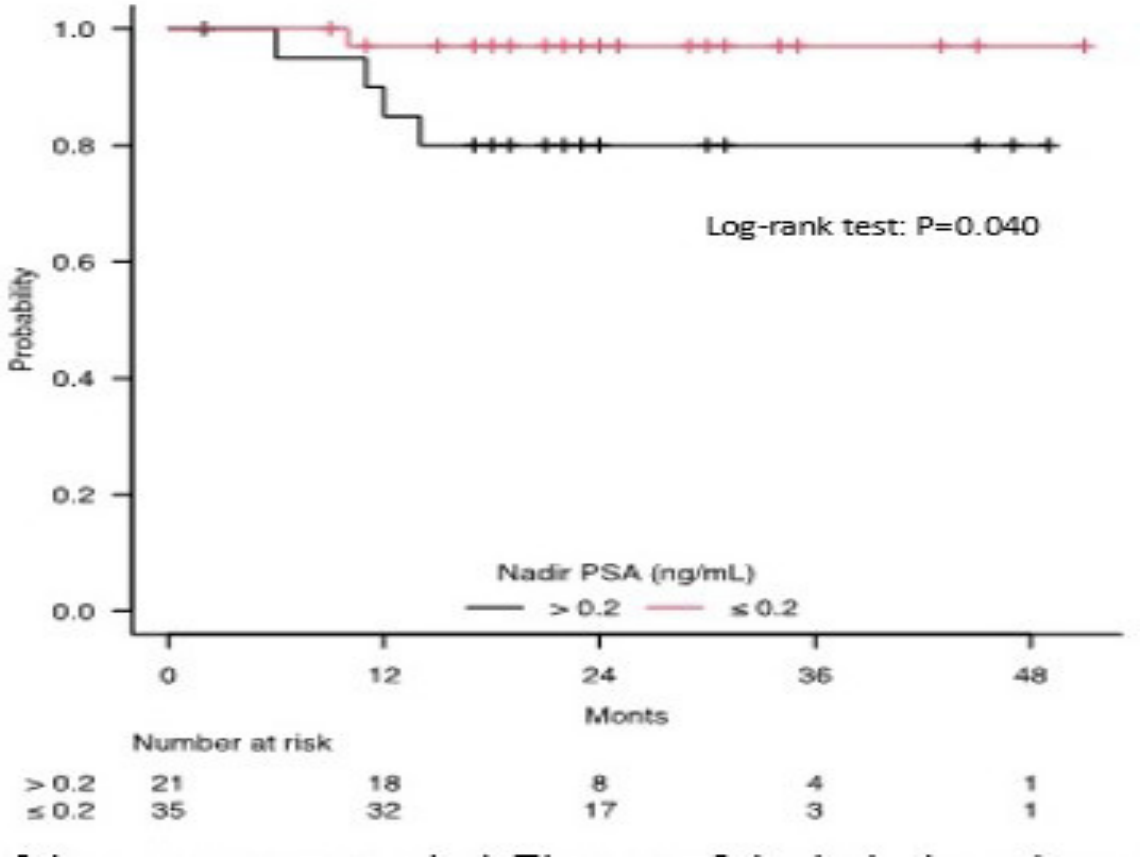

Figure 3. Prostate CSS comparison of nadir PSA > 0.2ng/mL or nadir PSA ≤ 0.2ng/mL in 3 months in the TAB group. The median CSS was not achieved in the nadir PSA ≤ 0.2 ng/mL group and was 33 months in the nadir PSA > 0.2 ng/mL group. There were no deaths in the nadir PSA ≤ 0.2 ng/mL group and 42 deaths in the PSA > 0.2 ng/mL group. Log-rank test was set at $P = .011$.

was applied to the data, and PSM resulted in 2 equally sized groups of 36 ARAT vs 36 TAB groups, with no residual statistically significant differences (**Table 2**), and 2 of 36 patients in the ARAT group and 13 of 36 patients in the TAB group died by prostate cancer. Based on Kaplan-Meier estimation, the median CSS was not reached in the ARAT group and 37 months in the bicalutamide group, and the 2-year CSS was 94.2% in the ARAT group and 68.8% in the TAB group, with a significant difference (log-rank test, $P = .006$; **Figure 1**). Univariate analysis revealed that pretreatment LDH level and TAB therapy were independent risk factors for CSS, and the HRs were 1.005 (95% CI: 1.001-1.010) and 6.138 (95% CI: 1.379-27.33). Multivariate analysis also revealed that LDH and TAB therapy were independent risk factors for CSS, and the HRS was 1.009 (95% CI: 1.002-1.016) and 11.09 (95% CI: 1.640-74.94) in this study (**Table S1**).

Progression-Free Survival

Disease progression was assessed by radiologic, clinical, or PSA progression or death. There were 11 of 56 in the ARAT group and 86 of 114 treatment failure events in the TAB group. After 1:1 PSM was applied, there were 7 of 36 and 25 of 36 treatment failure events, and the 2-year PFS rates were 77.5% and 25.7% in the ARAT and TAB groups, respectively. The median time to CRPC was NA in the ARAT group and 9 months in the TAB group, with a significant difference (log-rank test, $P < .001$; **Figure 2**).

Adverse Events

Seven patients in the ARAR group and two patients in the TAB group reported AEs of grade ≥ 3 based on Common Terminology Criteria for Adverse Events version 5.0 (Table S2 in the Supplementary Appendix). Among them, one (2.6%) died due to hepatic failure induced by abiraterone during the follow-up period. We also encountered one case (2.6%) of grade 3 rhabdomyolysis, an extremely rare AE of abiraterone. Four cases (10.3%) were grade 3 aspartate aminotransferase (AST) increased with abiraterone. One (7.1%) grade 3 AST increase was reported in patients treated with enzalutamide. In the TAB group, two (1.8%) grade 3 AST increases were reported as AE.

Treatment After Progression

In the ARAT group, 11 patients experienced disease progression. 10 patients were treated with docetaxel, and 1 patient received enzalutamide after progression. Eighty-six men received secondary treatment after disease progression in the TAB group, and the post-treatment details are shown in Table S3. Fifty-five patients in the bicalutamide group underwent ARAT after acquiring CRPC.

Subgroup Analysis

We compared whether the achievement of PSA, which became ≤ 0.2 ng/mL, in 3 months could affect the CSS in both groups. The achievement of PSA ≤ 0.2 at 3 months after initiation of systemic therapy was asso-

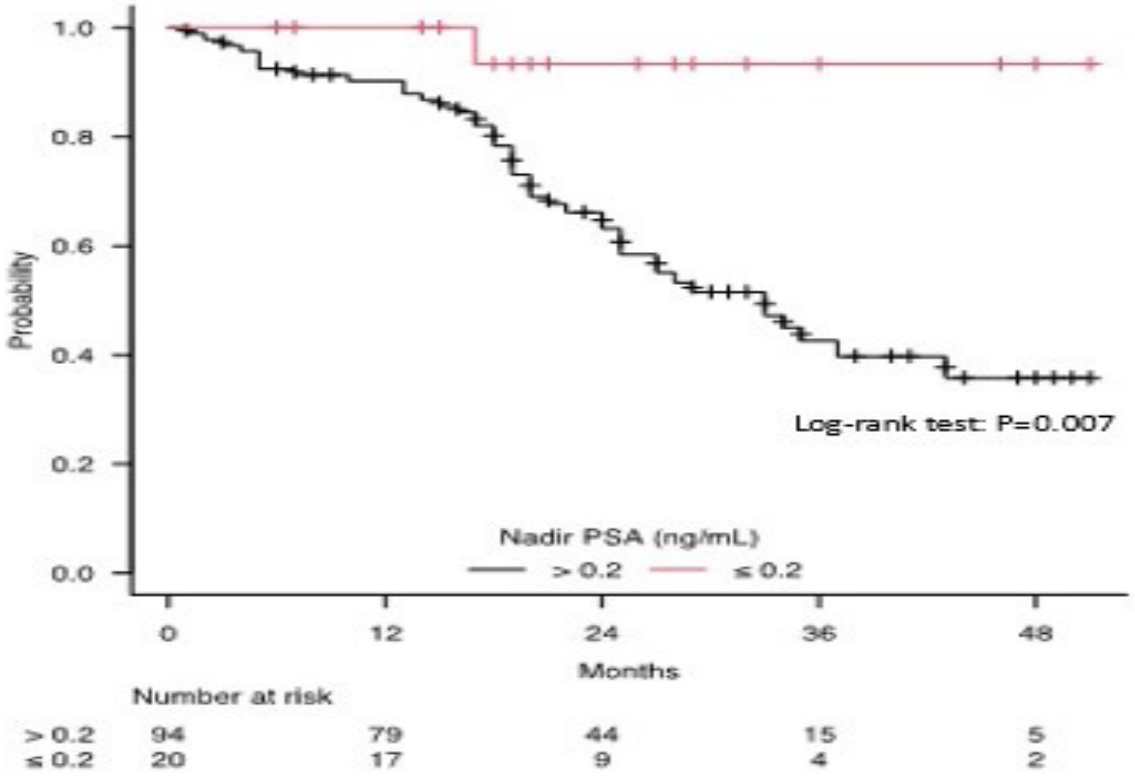

Figure 4. Prostate cancer specific survival comparison of nadir PSA > 0.2 ng/mL or nadir PSA ≤ 0.2 ng/mL in 12 months in TAB group.
Abbreviations: CSS, cancer-specific survival; PSA, prostate-specific antigen

ciated with better CSS in the TAB group(log-rank test, $P = .011$; **Figure 3**) but the values were statistically insignificant in the ARAT group (log-rank test, $P = .42$; **Figure S1**). The demographic characteristics of both patients in the ARAT group showed statistically significant differences in BSI (**table S4**), and the demographic characteristics of both patients in the TAB group were statistically different in initial PSA, BSI, baseline Hb level, and presence of visceral metastasis (**Table 3**).

DISCUSSION

This is a retrospective real-world study comparing the efficacy and safety of upfront ARAT in addition to ADT and those of bicalutamide with ADT in patients with high-volume mHSPC in multiple centers in Japan. This is the first study to reveal that upfront ARAT for patients with high-volume mHSPC significantly prolongs CSS and PFS when compared with TAB, and the number of PSA level reductions significantly prolongs CSS in both groups.

In Japan, TAB treatment for high-volume mHSPCs is often performed in daily clinical practice. There are several possible explanations for this finding. One of the reasons for the use of bicalutamide in men with high-volume mHSPC is that there was no significant difference in OS between the ARAT and ADT groups in the Japanese subgroup in the LATITUDE, ARCHES, or TITAN trials, even though the HRs of OS were similar to those of the entire group.[13–15] In addition, although the ENZAMET trials showed that the enzalutamide group had significantly prolonged OS when compared with the standard care group, the study did not include Japanese facilities.[5] Some studies have compared the efficacy and safety of up-front abiraterone and bicalutamide for de novo high-volume mHSPC in Japanese patients.[10,11] All these studies reveal that abiraterone significantly prolongs PFS or time to CRPC compared to bicalutamide, consistent with the results of this study. However, previous studies do not show the differences in CSS or OS between abiraterone and bicalutamide groups due to the short period of observation. This is the first study to also reveal a significant difference in the CSS and PFS of patients in the ARAT group, a treatment that included abiraterone, enzalutamide, and apalutamide compared to the TAB group in a real-world sample from multiple centers in Japan. Our study also implied that the grade ≥ 3 AEs of ARAT were more frequent than those of TAB; therefore, more attention should be paid to monitoring AEs in ARAT in daily clinical practice. Especially when using ARAT, AST and ALT levels have to be monitored by blood tests to assess hepatic damage to the patients.

Other studies showed significant differences in OS when the PSA reaches a certain level after initial treatment.[16,17] We assessed how the CSS was affected when nadir PSA of ≤ 0.2 ng/mL was reached in 3 months. The Kaplan-Meier estimation of both groups showed that there are significant differences in CSS between patients with nadir PSA of ≤ 0.2 ng/mL and patients with nadir PSA of > 0.2 ng/mL in the TAB group but there were no significant differences in ARAT group. The demographic characteristics showed that initial PSA, BSI, initial Hb level, and presence of visceral metastases were potential indicators for achieving nadir

PSA of ≤ 0.2 ng/mL in 3 months in the TAB group. If patients with high-volume mHSPC who are undergoing treatment with TAB change to ARAT when the nadir PSA ≤ 0.2 ng/mL in 3 months is not achieved, more benefits may be achieved.

This study has some limitations. First, this was not a randomized retrospective study. Although we applied PSM analysis to adjust for possible confounders, this approach does not account for randomization. Second, the number of patients and follow-up period were limited. In particular, there were only seven participants who had CRPC in the ARAT group. Hence, it remains unclear whether the CSS of the bicalutamide group cases receiving ARAT after CRPC could match that of the ARAT group.

CONCLUSIONS

Upfront ARAT with ADT significantly prolonged CSS and PFS compared to TAB in de novo high-volume mHSPC patients in Japan; however, careful attention should be paid to AEs. Further investigation with a longer follow-up period is still needed on CSS after CRPC in both groups. These data suggest that upfront ARAT can be more beneficial for patients with de novo high-volume mHSPC than TAB.

CONFLICT ON INTEREST

The authors declare that they have no conflicts of interest.

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