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Original Article

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Triplet therapy with darolutamide and docetaxel for metastatic castration-sensitive prostate cancer: a multicenter real-world study

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Abstract

Background: **Triplet therapy with darolutamide and docetaxel has reshaped the treatment landscape of metastatic castration-sensitive prostate cancer (mCSPC). However, real-world evidence regarding its oncological outcomes and toxicity remains limited.**

Methods: **We retrospectively reviewed 112 consecutive patients with mCSPC who were treated with triplet therapy. A deep prostate-specific antigen (PSA) response was defined as a PSA level < 0.2 ng/ml or a ≥ 90% decline from baseline. Castration-resistant prostate cancer (CRPC)-free survival was used as the survival endpoint. Clinicopathological factors associated with CRPC-free survival were analysed using a Cox proportional hazards model. Treatment-related adverse events (AEs) were comprehensively documented by type and grade.**

Results: **During a median follow-up of 17.1 months, 15 patients developed CRPC and four died of prostate cancer; 1-year CRPC-free survival and overall survival rates were 89.8% (95% confidence interval, 83.9%–96.0%) and 98.8% (96.5%–100%), respectively. A deep PSA response was achieved in 73.2% of patients (PSA nadir <0.2 ng/ml) and in 96.4% (PSA ≥ 90% decline). In both the univariable and multivariable analyses, no baseline factor was significantly associated with CRPC-free survival. Grade ≥ 3 hematologic AEs occurred in 75.0% of patients. Among the 31 patients who discontinued docetaxel, 26 discontinued due to non-hematologic AEs.**

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Conclusions: **Triplet therapy demonstrated substantial clinical activity in real-world patients with mCSPC, with high rates of deep PSA response despite frequent AEs. These findings support the feasibility of triplet therapy in routine practice. Given the substantial toxicity burden, careful patient selection and proactive AE management remain important.**

Keywords castration, darolutamide, docetaxel, prostate cancer, triplet therapy

Introduction

Triplet therapy combining docetaxel and an androgen receptor pathway inhibitor (ARPI) with androgen deprivation therapy has significantly improved outcomes in patients with metastatic castration-sensitive prostate cancer (mCSPC). Two phase III randomized controlled trials, ARASENS and PEACE-1, demonstrated that the addition of an ARPI (darolutamide or abiraterone) to androgen deprivation therapy plus docetaxel significantly prolonged overall survival (OS) compared with androgen deprivation therapy plus docetaxel alone [1–4]. In particular, the ARASENS trial reported a 32.5% reduction in the risk of death with the addition of darolutamide [3, 4]. Given the intratumoral heterogeneity of mCSPC [5], treatment strategies that combine agents with different mechanisms of action from the outset are considered a rational approach to suppress the emergence of resistant clones and maximize therapeutic efficacy [6]. Accordingly, triplet therapy is currently recommended as a standard treatment option for patients with high-risk or high-volume mCSPC [1, 7–9]. On the other hand, major concerns regarding triplet therapy in clinical practice include hematologic and non-hematologic adverse events (AEs) associated with docetaxel, which may lead to treatment discontinuation and/or dose reduction, ultimately reducing treatment intensity [10–15]. However, real-world evidence on the oncological outcomes and toxicity of triplet therapy remains limited, particularly in large-scale cohorts [9]. Therefore, this study aimed to comprehensively evaluate the effectiveness and safety of triplet therapy with darolutamide and docetaxel in a multicenter real-world cohort of 112 patients with mCSPC.

Patients and methods

Patients, treatments, and study design

This multicenter retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (approval number: 2024246NI-(2)), as well as that of each participating institution. Given the retrospective nature of the study, the requirement for written informed consent was waived by the board. An opt-out approach was used to obtain informed consent from patients.

We retrospectively reviewed the clinical records of patients with mCSPC who received triplet therapy at 12 affiliated institutions, including seven university hospitals, between 2023 and 2025. Patients with a follow-up period of less than 3 months after the initiation of triplet therapy were excluded to ensure adequate evaluation of early clinical outcomes. The final analysis included 112 consecutive patients with pathologically confirmed prostate cancer who were treated with triplet therapy.

Triplet therapy generally consisted of androgen deprivation therapy (medical or surgical), darolutamide (1200 mg/day), and six cycles of docetaxel (75 mg/m^2 every 3 weeks) [3]. Dose reductions were made according to institutional policy or at the physician's discretion, based on the patient's condition. The timing and sequence of darolutamide and docetaxel initiation were determined at the discretion of the treating physician based on individual patient characteristics and clinical circumstances.

Data collection, definitions, and endpoints

Patient characteristics, including age, body mass index, Eastern Cooperative Oncology Group performance status, and baseline prostate-specific antigen (PSA) levels, were retrospectively collected for all 112 patients. Disease volume was classified as high or low according to the CHAARTED criteria [16], with high volume defined as the presence of visceral metastases or ≥ 4 bone lesions, including at least one beyond the spine and pelvis. Similarly, disease risk was assessed using the LATITUDE criteria [17]; patients meeting at least two of the following three criteria—Gleason score ≥ 8, ≥ 3 bone lesions, or measurable visceral metastases—were classified as high risk.

A deep PSA response was defined as a PSA level < 0.2 ng/ml or a $\geq 90\%$ decline from baseline. Castration-resistant prostate cancer (CRPC)-free survival was used as the survival endpoint and was defined as the time from treatment initiation to biochemical progression, clinical progression, or death from any cause.

Treatment-related AEs were comprehensively documented by type and grade according to the Common Terminology Criteria for Adverse Events (version 5.0). AE-related discontinuation was defined as the discontinuation of docetaxel due to treatment-related AEs, rather than disease progression.

Statistical analysis

CRPC-free survival and OS were estimated using the Kaplan–Meier method and compared using the log-rank test, as appropriate. Associations between clinicopathological parameters and CRPC-free survival were assessed using a Cox proportional hazards model. Continuous variables were compared using Welch's *t*-test, and categorical variables were assessed using Fisher's exact test. All statistical analyses were performed using R version 4.5.0. Statistical significance was defined as $P < .05$.

Results

Patient characteristics and treatment details

Patient characteristics are summarized in Table 1. Bone was the most common site of metastasis (83.9%), followed by lymph nodes (49.1%), lung (17.9%), and liver (5.4%). According to the CHAARTED and LATITUDE criteria, 68.8% and 71.4% of patients

Table 1 Patient characteristics (n = 112).

Parameter	Value
Age, years, median (IQR)	72 (68–76)
Body mass index, kg/m^2, median (IQR)	23.0 (21.3–25.6)
ECOG performance status, *n* (%):	
0	84 (75.0)
≥ 1	28 (25.0)
Charlson comorbidity index, *n* (%):	
0	71 (63.4)
≥ 1	41 (36.6)
Age-adjusted Charlson comorbidity index, median (IQR)	3 (2–4)
Initial PSA level, ng/ml, median (IQR)	259 (51–797)
Alkaline phosphatase, U/L, median (IQR)	178 (81–392)
Gleason score, *n* (%):	
≤ 7	7 (6.3)
8	37 (33.0)
≥ 9	65 (58.0)
Other/Unknown	3 (2.7)
Metastatic site, *n* (%):	
Bone metastasis	94 (83.9)
Lymph node metastasis	55 (49.1)
Lung metastasis	20 (17.9)
Liver metastasis	6 (5.4)
CHAARTED criteria, *n* (%):	
High volume	77 (68.8)
Low volume	35 (31.3)
LATITUDE criteria, *n* (%):	
High risk	80 (71.4)
Low risk	32 (28.6)
EOD score, *n* (%):	
0	20 (17.9)
1–2	48 (42.9)
3–4	44 (39.3)
Type of metastatic disease, *n* (%):	
De novo	102 (91.1)
Recurrent	10 (8.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EOD, extent of disease; IQR, interquartile range; PSA, prostate-specific antigen.

were classified as having high-volume and high-risk disease, respectively. Most patients (91.1%) had *de novo* disease, while the remaining 8.9% had recurrent disease.

The details of triplet therapy administration are summarized in Table 2. Overall, darolutamide was well tolerated. Almost all patients (98.2%) initiated treatment at the full dose (1200 mg/-day). Dose reduction during treatment was required in 19 patients (17.0%), and treatment discontinuation due to AEs occurred in 16 patients (14.3%). In contrast, docetaxel administration required more individualized adjustments. The standard dose (75 mg/m^2) was initiated in 79 patients (70.5%), while a reduced dose (< 75 mg/m^2) was used in 33 patients (29.5%). Dose reduction during treatment was required in 28 patients (25.0%), and discontinuation due to AEs occurred in 29 patients (25.9%). Of the 112 patients, 79 (70.5%) completed all six cycles of docetaxel.

Table 2 Details of triplet therapy administration (n = 112).

Parameter	Value
Initial dose of darolutamide, *n* (%)	
1200 mg/day	110 (98.2)
600 mg/day	2 (1.8)
Dose reduction of darolutamide, *n* (%)	19 (17.0)
Discontinuation of darolutamide due to AEs, *n* (%)	16 (14.3)
Initial dose of docetaxel, *n* (%)	
75 mg/m^2	79 (70.5)
70 mg/m^2	22 (19.6)
< 70 mg/m^2	11 (9.8)
Dose reduction of docetaxel, *n* (%)	28 (25.0)
Total cycles of docetaxel, *n* (%):	
6 cycles	77 (68.8)
4–5 cycles	18 (16.1)
1–3 cycles	17 (15.2)
Discontinuation of docetaxel due to AEs, *n* (%)	31 (27.7)
Prednisolone during chemotherapy, *n* (%)	11 (9.8)
Use of G-CSF during chemotherapy, *n* (%)	105 (93.8)
Sequence of agents, *n* (%)	
Docetaxel first	4 (3.6)
Darolutamide first, > 30 days)	11 (9.8)
Darolutamide first, ≤ 30 days)	50 (44.6)
Simultaneous	47 (42.0)
Darolutamide-to-docetaxel interval, days	6 (0–21)

Abbreviations: AE, adverse event; G-CSF, granulocyte colony stimulating factor.

Table 3 PSA responses to triplet therapy (n = 112).

Parameter	Value
Relative PSA response, *n* (%):	
PSA decline ≥90% at 3 months	85 (76.6)
PSA decline ≥90% at 6 months[a]	92 (86.8)
PSA decline ≥90% overall	108 (96.4)
Absolute PSA response, *n* (%):	
PSA < 0.2 ng/ml at 3 months	31 (27.9)
PSA < 0.2 ng/ml at 6 months[a]	57 (54.3)
PSA nadir <0.2 ng/ml	82 (73.2)
PSA nadir, ng/mL, median (IQR)	0.04 (0.01–0.67)

Abberviations: IQR, interquartile range; PSA, prostate specific antigen. [a]PSA at 6 months was available for 107 patients.

Treatment effectiveness and factors associated with survival

PSA responses to triplet therapy are summarized in Table 3. A deep PSA response was achieved in 73.2% of patients (PSA nadir <0.2 ng/ml) and in 96.4% (PSA ≥ 90% decline).

During a median follow-up of 17.1 months, 15 patients developed CRPC and four died of prostate cancer. Figure 1 presents Kaplan–Meier curves for CRPC-free survival and OS; the median survival was not reached for either endpoint; 1-year CRPC-free survival and OS rates were 89.8% (95% confidence interval, 83.9%–96.0%) and 98.8% (96.5%–100%), respectively.

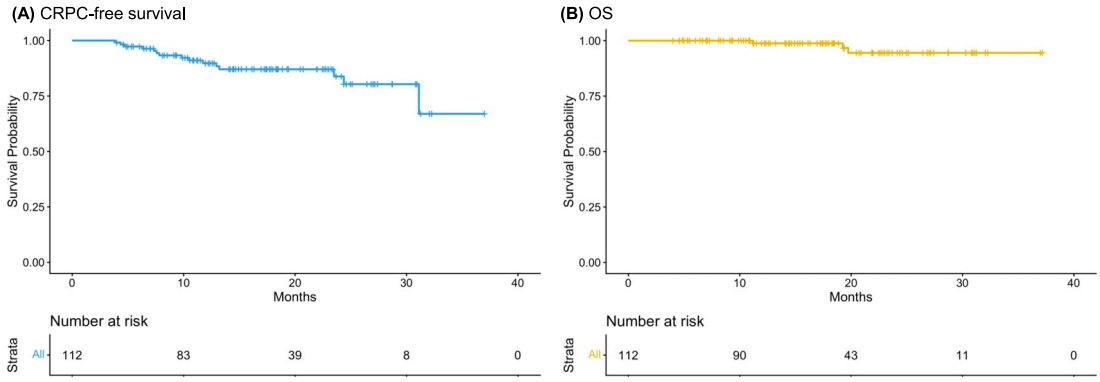


Figure 1 Kaplan–Meier curves depicting (A) CRPC-free survival and (B) OS in all 112 patients treated with triplet therapy. CRPC, castration-resistant prostate cancer; OS, overall survival.

Figure 2 shows Kaplan–Meier curves for CRPC-free survival and OS stratified by disease volume according to the CHAARTED criteria and by disease risk according to the LATITUDE criteria. For CRPC-free survival, no significant differences were observed between high- and low-volume disease or between high- and low-risk disease. Similarly, no significant differences in OS were observed between these groups. However, as no deaths occurred in the low-volume or low-risk groups, patients with high-volume and high-risk disease showed a numerical trend toward higher mortality compared with their respective counterparts.

Table 4 presents the results of the univariable and multivariable Cox proportional hazards analyses for CRPC-free survival based on pretreatment clinical parameters. In both the univariable and multivariable analyses, no baseline factor was significantly associated with CRPC-free survival. These findings suggest that no robust pretreatment predictor of CRPC-free survival was identified in this cohort.

As an exploratory analysis, we evaluated the association between docetaxel treatment exposure and CRPC-free survival (Supplementary Fig. S1). Initial docetaxel dose (75 mg/m^2 vs. $<$75 mg/m^2) was not significantly associated with CRPC-free survival (Supplementary Fig. S1A). Although patients who completed six cycles of docetaxel appeared to have longer CRPC-free survival in the conventional Kaplan–Meier analysis, the difference was not statistically significant (Supplementary Fig. S1B). Furthermore, the apparent association was attenuated in a 6-month landmark analysis designed to account for immortal time bias (Supplementary Fig. S1C).

Safety profile and factors associated with AE-related discontinuation of docetaxel

Table 5 summarizes AEs in the overall population (n = 112). Grade $\geq$ 3 AEs occurred in 90 patients (80.4%), most commonly neutropenia, which was observed in 83 patients (74.1%). Granulocyte colony-stimulating factor was administered in 105 patients (93.8%) during chemotherapy. Hematologic AEs, including neutropenia, were frequent and pronounced but generally manageable and rarely led to docetaxel discontinuation. In contrast, grade $\geq$ 3 non-hematologic AEs were observed in 23 patients (20.5%). Fluid retention–related complications, such as edema and pleural or ascitic effusions, were prominent. Notably, one case of grade 3 macular edema, a rare but serious ophthalmologic complication, was observed. The frequencies of treatment discontinuation attributable to individual AEs are summarized in the right half of Table 5. Among the 31 patients who discontinued docetaxel, 26 discontinued due to non-hematologic AEs. Severe conditions included interstitial lung disease, acute respiratory distress syndrome, and stroke. Fluid retention-related AEs led to discontinuation in four patients.

After excluding two cases of docetaxel discontinuation due to early disease progression, we exploratorily compared the characteristics of patients with and without AE-related discontinuation of docetaxel (n = 110; Table 6). Patients with AE-related discontinuation were significantly older than those without. No significant differences were observed in the initial docetaxel dose or in the rate of dose reduction during treatment. In this exploratory analysis, concomitant prednisolone (PSL) use was less frequent among patients with AE-related discontinuation than among those without discontinuation (P = .035). Given the limited number of patients receiving PSL, this finding should be considered hypothesis-generating and interpreted with caution.

Discussion

This study evaluated the effectiveness and safety of triplet therapy for mCSPC in one of the largest real-world cohorts reported to date. Among the 112 patients included, triplet therapy demonstrated substantial effectiveness in real-world practice, as evidenced by a high rate of deep PSA responses and favorable CRPC-free survival and OS. Completion of six cycles of docetaxel was associated with prolonged CRPC-free survival. However, triplet therapy was also associated with a high incidence of AEs, including hematologic toxicities such as neutropenia and non-hematologic toxicities such as edema and pleural or ascitic effusions. Exploratory analyses further suggested that concomitant use of PSL was significantly associated with a reduced rate of AE-related discontinuation of docetaxel. These findings provide additional insights into the real-world use of triplet therapy in patients with mCSPC.

The effectiveness of triplet therapy observed in this study was highly consistent with the results of the ARASENS trial [3], particularly in reproducing the high rate of deep PSA responses. An early deep PSA response is recognized as a key prognostic

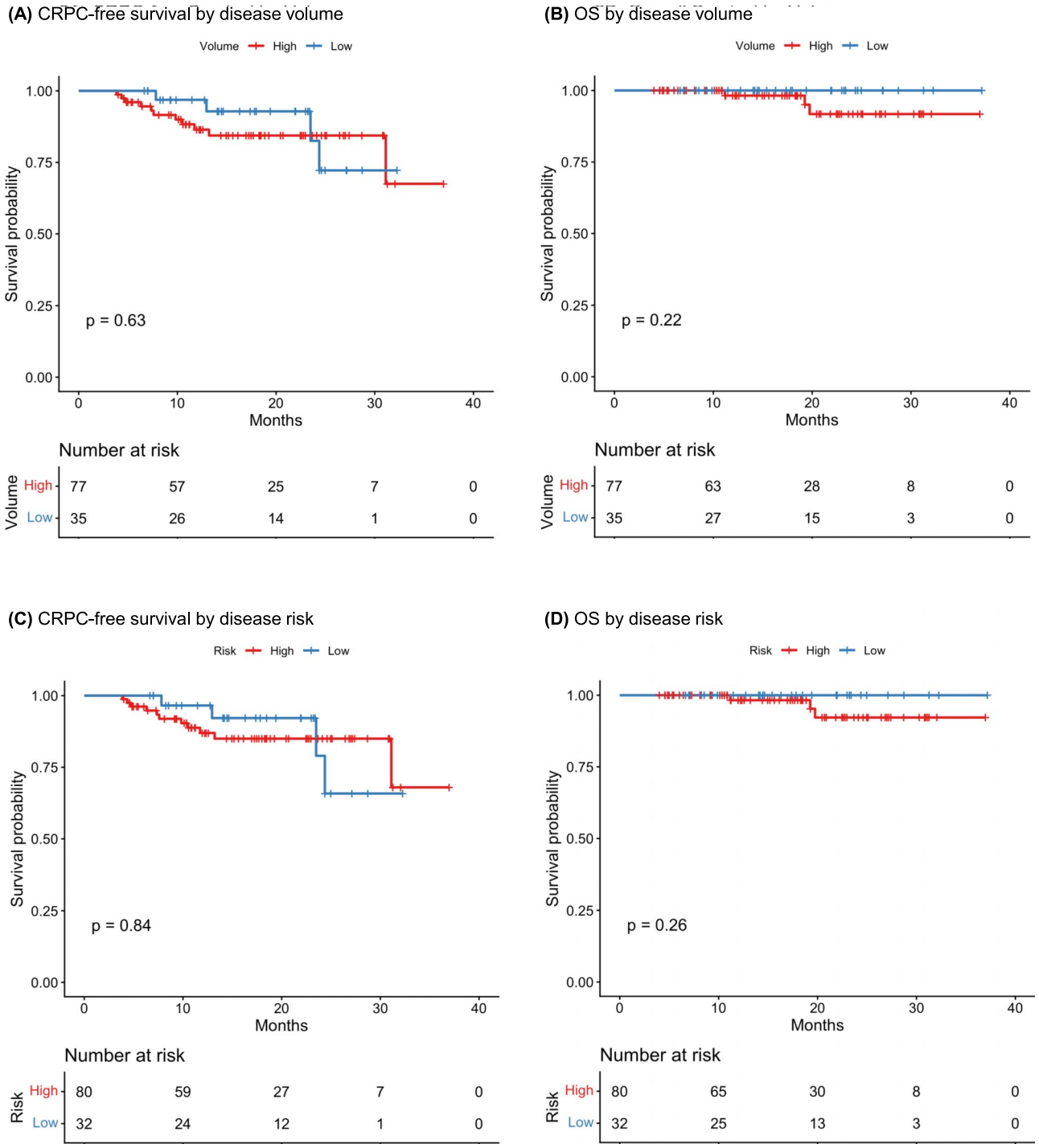


Figure 2 Kaplan–Meier curves depicting (A) CRPC-free survival and (B) OS by disease volume according to the CHAARTED criteria and those depicting (C) CRPC-free survival and (D) OS by disease risk according to the LATITUDE criteria. CRPC, castration-resistant prostate cancer; OS, overall survival.

indicator in mCSPC; an analysis of the TITAN trial demonstrated a strong association between achieving PSA $<$ 0.2 ng/ml and improved long-term survival outcomes [18]. In the latest ARASENS analysis, 67% of patients in the darolutamide group achieved this threshold [19, 20], whereas a higher proportion of patients in our cohort (73.2%) reached PSA $<$ 0.2 ng/ml. Furthermore, 96.4% of patients achieved a $\geq$ 90% decline in PSA, indicating robust deep PSA responses to triplet therapy in the real-world setting. Although the follow-up duration remains relatively short, survival outcomes in our cohort appear favorable, with the median CRPC-free survival and OS not yet reached.

The safety profile of triplet therapy in our cohort revealed a high incidence of AEs related to hematologic toxicity and fluid retention, underscoring the need for careful management. In the ARASENS trial [3], grade $\geq$ 3 neutropenia occurred in 33.7% of patients, whereas it occurred in 74.1% of patients

Table 4 Univariate and multivariate cox proportional hazards analyses of pretreatment clinical parameters for CRPC-free survival.

Parameter	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age						
$<$ 72 years	Ref.			Ref.		
$\geq$ 72 years	0.72	0.26, 2.0	0.52	0.62	0.21, 1.82	0.38
ECOG performance status						
0	Ref.			Ref.		
$\geq$ 1	1.10	0.348, 3.45	0.88	1.40	0.39, 5.07	0.61
CCI						
0	Ref.			Ref.		
$\geq$ 1	0.96	0.33, 2.81	0.93	0.79	0.24, 2.60	0.70
Initial PSA	1.00	1.00, 1.00	0.34	1.00	1.00, 1.00	0.37
Gleason score[a]	1.13	0.57, 2.24	0.72	1.37	0.64, 2.93	0.42
High volume	1.30	0.41, 4.11	0.65	1.39	0.38, 5.08	0.62
Visceral metastasis						
No	Ref.			Ref.		
Yes	1.50	0.476, 4.71	0.49	1.65	0.45, 6.11	0.45
Type of metastatic disease						
De novo	Ref.			Ref.		
Recurrent	2.10	0.467, 9.48	0.33	2.52	0.45, 14.1	0.29

Abbreviations: CI, confidence interval; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PSA, prostate-specific antigen. [a]Gleason score was available for 109 patients.

Table 5 Summary of AEs of triplet therapy (n = 112).

AE	Any grade	Grade $\geq$ 3	Docetaxel discontinuation due to AE	Darolutamide discontinuation due to AE
All, *n* (%):	107 (95.5)	90 (80.4)		
Hematological, *n* (%):	89 (79.5)	84 (75.0)		
Neutropenia	88 (78.6)	83 (74.1)	4 (3.6)	2 (1.8)
Febrile neutropenia	10 (8.9)	10 (8.9)		
Anemia	4 (3.6)	3 (2.7)		
Thrombocytopenia	2 (1.8)	1 (0.9)	1 (0.9)	
Non-hematological, *n* (%):	80 (71.4)	23 (20.5)		
Diarrhea	12 (10.7)	0 (0.0)		
Dysgeusia	9 (8.0)	0 (0.0)		
Decreased appetite	7 (6.2)	2 (1.8)	2 (1.8)	
Gastrointestinal hemorrhage	2 (1.8)	2 (1.8)	1 (0.9)	
Fatigue	31 (27.7)	3 (2.7)	3 (2.7)	2 (1.8)
Peripheral neuropathy	20 (17.9)	1 (0.9)	2 (1.8)	1 (0.9)
Rash	19 (17.0)	4 (3.6)	3 (2.7)	3 (2.7)
Alopecia	17 (15.2)	0 (0.0)		
Edema	22 (19.6)	3 (2.7)	3 (2.7)	1 (0.9)
Macular edema	1 (0.9)	1 (0.9)	1 (0.9)	
Pleural/ascites effusions	5 (4.5)	0 (0.0)		
Elevated liver function tests	10 (8.9)	5 (4.5)	3 (2.7)	3 (2.7)
Stomatitis	6 (5.4)	0 (0.0)		
Infusion reaction	3 (2.7)	0 (0.0)	2 (1.8)	
Interstitial lung disease	2 (1.8)	1 (0.9)	2 (1.8)	
Acute respiratory distress syndrome	1 (0.9)	1 (0.9)	1 (0.9)	
Dyspnea	1 (0.9)	1 (0.9)	1 (0.9)	
Stroke	1 (0.9)	1 (0.9)	1 (0.9)	
Tumor lysis syndrome	1 (0.9)	1 (0.9)		
Dizziness	2 (1.8)	0 (0.0)	1 (0.9)	1 (0.9)

Abbreviation: AE, adverse event.

Table 6 Comparison between patients with and without AE-related discontinuation of docetaxel (n = 110).

Parameter	With AE-related discontinuation (n = 31)	Without AE-related discontinuation (n = 79)	P-value
Age, years, median (IQR)	74 (70–79)	71 (66–75)	0.013[a]
ECOG PS, n (%)			0.15[b]
0	20 (64.5)	62 (78.5)	
≥ 1	11 (35.5)	17 (21.5)	
Initial PSA level, ng/ml, median (IQR)	133.0 (48.1–641.0)	316 (51.7–982.0)	0.19[a]
High volume, n (%)	19 (61.3)	57 (72.2)	0.36[b]
Initial dose of docetaxel, n (%)			0.11[b]
75 mg/m^2	23 (74.2)	55 (69.6)	
70 mg/m^2	3 (9.7)	19 (24.1)	
< 70 mg/m^2	5 (16.1)	5 (6.3)	
Dose reduction of docetaxel, n (%)	7 (22.6)	21 (26.6)	0.81
Use of PSL, n (%)	0 (0.0)	11 (13.9)	0.032[b]

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PSL, prednisolone. [a]Welch's t-test; [b]Fisher's exact test.

in our cohort. Furthermore, the rates of treatment discontinuation due to AEs were 14.3% for darolutamide and 25.9% for docetaxel. Fluid retention-related AEs were also notable, including edema (19.6%) and pleural or ascitic effusions (4.5%). We additionally encountered a case of grade 3 macular edema, a serious ophthalmologic complication with direct impact on visual function. Compared with conventional doublet therapies (ARPI or docetaxel plus androgen deprivation therapy), these findings may be attributable to a synergistic effect of ARPI and docetaxel. In real-world clinical practice, older patients with comorbidities are more frequently treated than in clinical trials. Given the narrow therapeutic window of docetaxel in such elderly and/or frail populations, the tolerability of triplet therapy can be challenging, necessitating close monitoring and meticulous management of AEs. These findings highlight the importance of appropriate patient selection and proactive toxicity management when considering triplet therapy in real-world clinical practice.

In the multivariable analysis of this study (n = 112), the number of docetaxel cycles was identified as the only independent predictor of CRPC-free survival, underscoring the importance of completing all six cycles of docetaxel. In the exploratory analysis excluding two cases with early disease progression (n = 110), patients who discontinued docetaxel due to AEs were significantly older than those who did not. Furthermore, PSL use was significantly associated with a lower rate of AE-related discontinuation, suggesting that appropriate supportive care may be critical for managing the toxicity of triplet therapy. Although PSL use was limited in this cohort and warrants cautious interpretation—particularly with respect to tolerability in elderly patients—concomitant PSL use may represent a promising strategy to improve treatment completion rates in triplet therapy, as has been observed in the CRPC setting [21].

This study has several limitations, including its retrospective design and relatively short follow-up period. In addition, the cohort was ethnically homogeneous (i.e. Japanese), which may limit the generalizability of the findings to other populations and healthcare settings, particularly with respect to differences in treatment tolerability and AE profiles. Nevertheless, this study represents one of the largest real-world investigations of triplet therapy to date and provides valuable additional evidence in this field.

Conclusion

Triplet therapy demonstrated substantial effectiveness in a real-world cohort of 112 patients with mCSPC with high rates of deep PSA response despite a considerable incidence of treatment-related AEs. These findings support the effectiveness of triplet therapy in routine clinical practice. Careful patient selection and proactive AE management may be important to maximize treatment benefit and maintain treatment continuity.

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Author contributions

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Supplementary material

Supplementary material are available at *Japanese Journal of Clinical Oncology* online.

Conflict of interest statement

The authors declare no conflicts of interest.

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Data availability

The dataset analyzed in this study is available from the corresponding author upon reasonable request.

Ethics statement

This retrospective study was conducted in accordance with the Declaration of Helsinki, and was approved by the Institutional Review Board of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (approval number: 2024246NI-(2)), as well as that of each participating institution.

Consent

Given the retrospective nature of the study, the requirement for written informed consent was waived by the board. An opt-out approach was used to obtain informed consent from patients.

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