



# Therapeutic effects of the combined androgen blockade therapy versus luteinizing hormone-releasing hormone analog monotherapy in patients with hormone naïve metastatic prostate cancer: a multi-institutional comparative analysis

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**Background:** The clinical benefit of the combined androgen blockade (CAB) therapy over luteinizing hormone-releasing hormone analog (LH-RHa) monotherapy for hormone naïve metastatic prostate cancer (mHNPC) is unclear. Therefore, we retrospectively compare the effectiveness of CAB with the LH-RHa monotherapy on the prognosis of Japanese patients with mHNPC.

**Methods:** We retrospectively evaluated the prognosis of 517 patients diagnosed with mHNPC between August 2001 and May 2017. The patients' data were obtained from the Michinoku Urological Cancer Research Group database and Hirosaki University-related hospitals. Patients were divided into the CAB and LH-RHa monotherapy groups based on primary androgen deprivation therapy (ADT). Overall survival (OS), cancer-specific survival (CSS), and castrate-resistant prostate cancer-free survival (CRPC-FS) were compared between the two groups using the Kaplan-Meier curve analysis. Inverse probability of treatment weighting (IPTW)-adjusted Cox hazard proportional analyses was performed to investigate the effect of primary ADT on oncological outcomes.

**Results:** The median age was 73 years old. The numbers of patients in the CAB and LH-RHa monotherapy groups were 447 and 70, respectively. The Kaplan-Meier curve analysis showed no significant differences in either 5-year OS (56.7% vs. 52.5%,  $P=0.277$ ), CSS (61.1% vs. 56.4%,  $P=0.400$ ), and CRPC-FS (33.1% vs. 31.1%,  $P=0.529$ ) between the groups. IPTW-adjusted multivariate Cox hazard proportional analyses showed no significant differences in OS, CSS, and CRPC-FS between the two groups.

**Conclusions:** No significant differences in oncological outcomes were observed between the CAB and LH-RHa monotherapy groups in patients with mHNPC.

**Keywords:** Metastatic prostate cancer; luteinizing hormone-releasing hormone analog (LH-RHa); combined androgen blockade (CAB); bicalutamide

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## Introduction

Prostate cancer is the common malignancy worldwide. In Japan, about 10% of patients with prostate cancer have distant metastases (1-3). For half a century, the standard for the initial treatment of hormone naïve metastatic prostate cancer (mHNPC) has been androgen deprivation therapy (ADT) (4). ADT includes orchiectomy, luteinizing hormone-releasing hormone analog (LH-RHa) therapy, and combined androgen blockade (CAB) including LH-RHa together with anti-androgen agents such as bicalutamide. Several guidelines do not recommend CAB therapy for patients with mHNPC as a first-line (5-7) therapy because no level 1 evidence supports the superiority of CAB as a primary treatment for mHNPC. In contrast, nearly 70% of mHNPC patients in Japan were treated initially with CAB (8) because a large-scale retrospective study suggested the advantage of using CAB to treat Japanese mHNPC. Nevertheless, there is no conclusive evidence suggesting which treatment is the optimal one as a baseline ADT for mHNPC (5-7). Although Japanese Urology Association (JUA) recommends CAB as one of the standard treatments (9), clinical benefits of CAB over the LH-RHa monotherapy are not understood.

In this study, we retrospectively compared the therapeutic effect of CAB with that of LH-RHa monotherapy as a primary treatment for mHNPC. We present the following article in accordance with the STROBE reporting checklist (available at: <http://dx.doi.org/10.21037/tau-20-966>).

## Methods

### *Study design and ethical statement*

We performed the present retrospective, multicenter study in accordance with the ethical standards outlined in the Declaration of Helsinki (revised in 2013). The ethics review boards of the Hirosaki University School of Medicine (authorization number: 2017-089) and all hospitals approved the protocol.

### *Setting and participants*

We evaluated data of patients with mHNPC who were initially treated with ADT obtained from multiple databases that included Michinoku Japan Urological Cancer Study Group database (from Hirosaki University Hospital, Akita University Hospital, Tohoku University Hospital, Yamagata University Hospital, Miyagi Cancer Center,

Yamagata Prefectural Central Hospital, Iwate Prefectural Isawa Hospital, Aomori Prefectural Central Hospital, and Sendai City Hospital) and from Hirosaki University-related hospitals' databases (from National Hospital Organization Hirosaki Hospital, Odate Municipal General Hospital, Mutsu General Hospital, Tsugaru General Hospital, and Aomori Rosai Hospital) between January 2001 and March 2019 (10-15). We defined mHNPC patients as prostate cancer patients with bone and/or distant lymph node metastasis and/or visceral metastases. Patients who received as initial treatment only the LH-RHa (leuporelin, goserelin acetate, or degarelix) were placed into the LH-RHa monotherapy group. CAB group was defined as a group of patients who received an initial treatment of LH-RHa combined with an anti-androgen medication such as bicalutamide.

### *Evaluation of variables*

We analyzed the following parameters: patients' age, Eastern Cooperative Oncology Group performance status (ECOG-PS), initial prostate-specific antigen (iPSA) levels at the time of cancer diagnosis, Gleason score (GS), extent of disease (EOD), and CHAARTED high-volume disease at the time of diagnosis. EOD were used to evaluate the extent of bone metastasis, the grades were EOD 0, normal or abnormal due to benign bone disease; EOD 1, <6 metastases; EOD 2, 6–20 metastases; EOD 3, >20 metastases but not a superscan; and EOD 4, superscan. CHAARTED high-volume disease was defined as the presence of visceral metastases or bone metastasis  $\geq 4$  with at least one bone metastasis must be present outside the vertebral bodies and pelvis in accordance with the CHAARTED study (16). Metastatic status was detected with computed tomography and bone scintigraphy before ADT. We also investigated the progression to castrate-resistant prostate cancer (CRPC), treatment history with docetaxel (DTX), abiraterone acetate (AA) and/or enzalutamide (ENZ), estramustine, and bone-modifying agents (BMA) during ADT treatment. The indication of these treatments according to the personal choice of the physician in charge of the case. The definition of CRPC in this study was based on the recommendations made by the prostate cancer clinical trial working group (17).

### *Treatment protocol*

All of the participating patients were treated initially with

ADT and/or BMA. After CRPC diagnosis, alternative anti-androgen therapy, estramustine, chemotherapy (DTX or CBZ), AA or ENZ were applied as treatment according to the personal choice of the physician in charge of the case.

### Statistical analysis

Statistical analysis of data was performed using SPSS software package version 24.0 (SPSS, Inc., Chicago, IL, USA), and R 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using either Fisher's exact test or the  $\chi^2$  test. Quantitative variables were expressed as median with interquartile range and compared statistically using the Mann-Whitney U test. P values <0.05 were considered as statistically significant. Patients with missing data were excluded from the analysis.

We analyzed overall survival (OS), which was defined as the time from start of ADT until all-cause death or last patient contact. Cancer-specific survival (CSS) was defined as the time from start of ADT until cancer death or last patient contact. CRPC-FS was defined as the time from start of ADT until progression toward CRPC. In addition, the PSA best response rate was assessed. Patients with missing PSA nadir data were excluded from the PSA best response rate analysis. PSA best response rate was defined as (iPSA – nadir PSA)/(iPSA). Oncological outcomes including OS, CSS, and CRPC-FS were investigated using the Kaplan-Meier method and compared with the log-rank test. We performed a Cox hazard proportional analysis using inverse probability of treatment weighting (IPTW) method to investigate the oncological outcomes for CAB and LH-RHa monotherapy groups considering background differences between the two groups (18). Variables included in the IPTW analysis were as follows: age, iPSA, ECOG-PS, GS, EOD, CHAARTED classification, treatment with DTX, AA and/or ENZ, estramustine, BMA.

## Results

### Baseline characteristics

We evaluated data of 809 Japanese patients with mHNPC who were initially treated with ADT obtained from multiple databases that included Michinoku Japan Urological Cancer Study Group database (n=667) and from Hiroasaki University-related hospitals' databases (n=142). We excluded 292 out of 809 participants because of either insufficient

data (n=213), or surgical castration monotherapy and anti-androgen monotherapy performed (n=79). After all the exclusion criteria were applied, we used data from 517 cases (CAB group had 447 cases, LH-RHa monotherapy group had 70 cases) in this study. Also, we excluded 60 cases for the CRPC-free survival (CRPC-FS) analysis (n=457) because of the lack of data (Figure 1).

Baseline patients' characteristics are shown in Table 1. The median age of patients was 73 years. The patient proportions of GS  $\geq$ 8, EOD  $\geq$ 2, CHAARTED high volume disease were 89%, 56%, and 63%, respectively. 303 patients developed CRPC and 160 patients died within a median follow-up period of 28 months. There were no significant differences between the two groups either in age, iPSA, GS, EOD, CHAARTED high-volume disease, or progression to CRPC. In contrast, there were significant differences in ECOG-PS (P=0.047), treatment with DTX (P=0.004), treatment with BMA (P=0.020), and follow-up period (P<0.001).

### Oncological outcomes

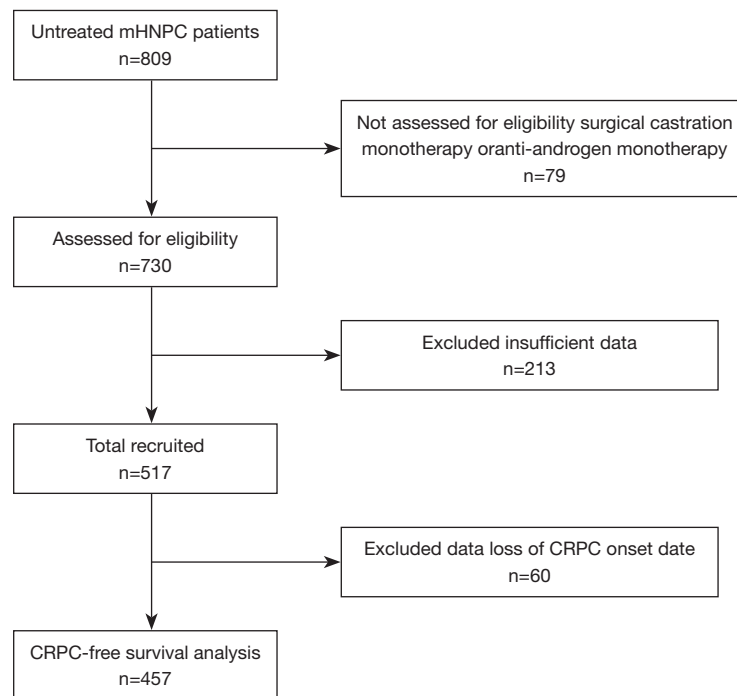
The Kaplan-Meier curve analysis showed no significant differences in either 5-year OS (Figure 2A, 56.7% vs. 52.5%, P=0.277), CSS (Figure 2B, 61.1% vs. 56.4%, P=0.400), or CRPC-free survival (Figure 2C, 33.1% vs. 31.1%, P=0.529) between the CAB and LH-RHa monotherapy groups. There is no significant difference in PSA best response rate (median: 99.5% vs. 99.8%, P=0.15, respectively, Figure S1).

### Uni- and multivariate analyses for prognosis

Univariate Cox hazard proportional analysis showed that CAB was not a significant predictor for OS, CSS, and CRPC-FS (Table 2). IPTW-adjusted multivariate Cox hazard proportional analyses showed no significant difference between CAB and LH-RHa monotherapy groups in either OS (P=0.132, HR 0.63, 95% CI, 0.38–1.06), CSS (P=0.384, HR 0.75, 95% CI, 0.41–1.36), or CRPC-FS (P=0.138, HR 0.71, 95% CI, 0.47–1.07) (Figure 3).

## Discussion

In this study, we compared the clinical outcomes of between two treatments: CAB and LH-RH monotherapy in the real-world practice in Japan and observed no statistically significant differences in either OS, CSS, or CRPC-FS



**Figure 1** Flow diagram for recruitment. The flow of study identification and exclusion. mHNPC, monotherapy for hormone naïve metastatic prostate cancer; CRPC, castrate-resistant prostate cancer.

between the two groups. Although several studies suggested the potential association between the racial differences and the efficacy of ADT (19,20), our results showed similar outcomes with those demonstrated for the patients from Western countries (21,22).

Previous meta-analysis comparing CAB and LH-RHa monotherapy for patients with mHNPC (6,821 men in 21 randomized trials) showed no significant differences in OS (21). Another meta-analysis (8,275 men in 27 randomized trials) showed that CAB may improve five-year OS up to 2.9% as compared with LH-RHa monotherapy in advanced prostate cancer ( $P=0.005$ ). However, while the participants of this meta-analysis included 12% of patients with locally advanced prostate cancer, there was no subgroup of patients with mHNPC included in this analysis (22). Due to the lack of evidence of CAB effectiveness for mHNPC treatment, several guidelines in Western countries do not recommend CAB for mHNPC as a first-line therapy (5-7). Our observations supports the guidelines recommendations used Western countries.

The randomized controlled trials (RCT) conducted in Japan failed to demonstrate the superiority of CAB

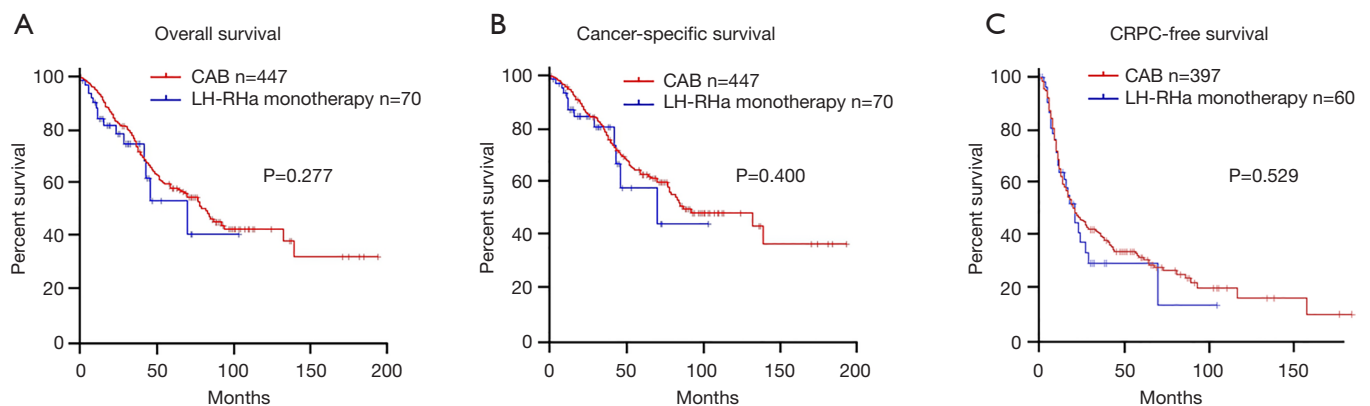
in patients with mHNPC (23). Also, in the largest retrospective study (J-CaP study) conducted in Japan in 2018, the therapeutic effect of LH-RHa monotherapy and CAB was examined by propensity score matching, but the superiority of CAB in mHNPC was not proven in subgroup analysis (24). Therefore, there is no high-level evidence to support the superiority of CAB over the LH-RHa monotherapy for men with mHNPC. Our results are in agreement with these studies conducted in Japan.

Why is 70% of mHNPC patients treated with CAB in Japan (8) without strong evidence of the superiority of CAB? It has to be debated why clinicians in Japan support the clinical benefits of CAB. First, clinicians may prescribe an anti-androgen agent combined with LH-RHa as an initial treatment to prevent testosterone “flare-up” phenomenon. It is believed that LH-RH agonists cause a transient rise in serum testosterone levels, and thereby induce “clinical flare” such as prostate cancer growth, increase bone pain, voiding problems, and spinal cord compression (25,26). European Association of Urology guideline states, “Offer initial short-term administration of antiandrogens to mHNPC patients treated with a LH-RH agonist to reduce the risk of the

**Table 1** Clinical characteristics of patients

Characteristics	All	CAB group	LH-RHa monotherapy group	P value
Number	517	447 [86]	70 [14]	
Age (years)	73 [65–78]	72 [65–78]	75 [64–79]	0.443
iPSA (ng/mL)	285 [63–855]	294 [62–896]	229 [71–589]	0.656
ECOG-PS				
0	300 [58]	253 [57]	47 [67]	0.047
1	153 [30]	141 [31]	12 [17]	
≥2	64 [12]	53 [12]	11 [16]	
Gleason score				
≤6	5 [1]	5 [1]	0 [0]	0.287
7	51 [10]	41 [9]	10 [14]	
≥8	461 [89]	401 [90]	60 [86]	
EOD ≥2	290 [56]	251 [56]	39 [56]	0.945
CHAARTED high-volume disease	327 [63]	280 [63]	47 [67]	0.509
Progression to CRPC	303 [59]	265 [59]	38 [54]	0.430
Treatment with DTX	130 [25]	122 [27]	8 [11]	0.004
Treatment with AA and/or ENZ	113 [22]	104 [23]	9 [13]	0.051
Treatment with estramustine	122 [24]	107 [21]	15 [21]	0.646
Treatment with BMA	288 [56]	258 [58]	30 [43]	0.020
follow-up period (months)	28 [13–52]	30 [14–54]	15 [9–31]	<0.001

Data are presented as median [IQR] or number [%]. IQR, interquartile range; iPSA, initial prostate-specific antigen; ECOG-PS, Eastern Cooperative Oncology Group performance status; EOD, extent of disease; CRPC, castration resistance prostate cancer; DTX, docetaxel; AA, abiraterone acetate; ENZ, enzalutamide; BMA, bone-modifying agents.



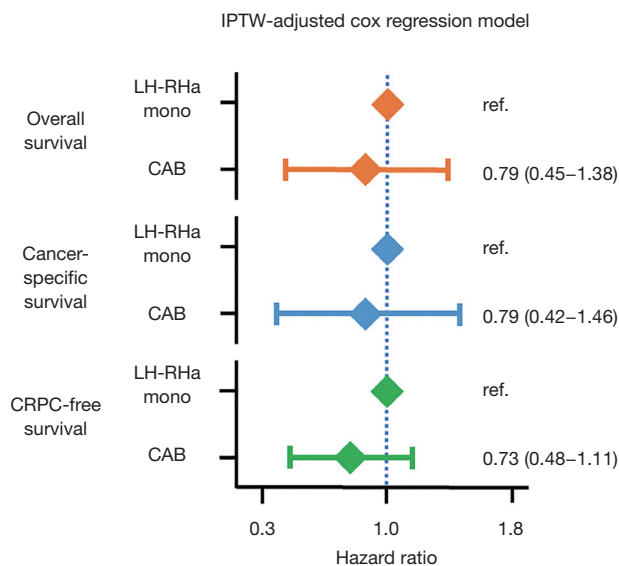
**Figure 2** Oncological outcomes between combined androgen blockade therapy (CAB) and luteinizing hormone-releasing hormone analog (LH-RHa) monotherapy. The 5-year overall survival (A), cancer specific survival (B), and castrate-resistant prostate cancer free survival (C) were compared between the CAB and LHRHa monotherapy.



**Table 2** Univariate and multivariate Cox hazard proportional analyses adjusted by inverse probability of treatment weighting (IPTW) model for prognosis

	Factor	P value	HR	95% CI
Univariate				
Overall survival	CAB	0.234	0.73	0.43–1.23
Cancer-specific survival	CAB	0.346	0.76	0.43–1.35
CRPC-free survival	CAB	0.247	0.81	0.57–1.16
Multivariate (IPTW analysis)				
Overall survival	CAB	0.442	0.79	0.45–1.38
Cancer-specific survival	CAB	0.480	0.79	0.42–1.46
CRPC-free survival	CAB	0.178	0.73	0.48–1.11

Inverse probability of treatment weighting analysis. IPTW model included variables; age, iPSA, ECOG-PS, GS, EOD, CHAARTED classification, treatment with DTX, AA and/or ENZ, estramustine, BMA. CRPC, castration resistance prostate cancer; CI, confidence interval; iPSA, initial prostate-specific antigen; ECOG-PS, Eastern Cooperative Oncology Group performance status; GS, Gleason score; EOD, extent of disease; DTX, docetaxel; AA, abiraterone acetate; ENZ, enzalutamide; BMA, bone-modifying agents.



**Figure 3** Multivariate Cox hazard proportional analysis adjusted by inverse probability of treatment weighting (IPTW) model for prognosis. IPTW-adjusted multivariate Cox hazard proportional analysis was performed to investigate the effect of combined androgen blockade on overall survival, cancer specific survival, and castrate-resistant prostate cancer free survival. Adjusted variables were age, iPSA, ECOG-PS, GS, EOD, CHAARTED classification, treatment with DTX, AA and/or ENZ, estramustine, BMA. iPSA, initial prostate-specific antigen; ECOG-PS, Eastern Cooperative Oncology Group performance status; GS, Gleason score; EOD, extent of disease; DTX, docetaxel; AA, abiraterone acetate; ENZ, enzalutamide; BMA, bone-modifying agents.

‘flare-up’ phenomenon” on weak evidence (6). Furthermore, clinicians should also be aware that several studies have failed to prove the existence of “flare-up” phenomenon (27-29). From this point of view, a short-term administration of antiandrogen would be enough to prevent testosterone “flare-up”.

Second, the efficacy of CAB in patients with mHNP can be misleading. Meta-analysis in Western countries (22), RCT in Japan (23), and large-scale observational studies in Japan (24) showed the superiority of CAB in advanced prostate cancer patients (including locally advanced prostate cancer). However, superiority of CAB was not observed in the subgroup analysis in mHNP. These results suggested the benefit of CAB might be limited in the locally advanced prostate cancer alone. Further study is necessary to clarify the superiority of CAB in those patients.

Recently, upfront therapy with abiraterone or DTX has been recommended for mHNP with high tumor burden (16,30). However, it remains unclear whether the benefit of CAB in the mHNP patients with the high tumor burden. Additional results suggested that effect of CAB on tumor burden might be limited. There was no significant difference in OS (Figure S2A) and CRPC-FS (Figure S2B) between the CAB and LHRHa monotherapy in the CHAARTED high group. Similarly, no significant difference was observed in OS (Figure S2C) and CRPC-FS (Figure S2D) between the CAB and LHRHa monotherapy in the CHAARTED low group. The IPTW-adjusted multivariate Cox regression analysis showed that OS and

CRPC-FS were not significantly different between the CAB and LHRHa monotherapy in regardless of tumor burden (Figure S3). However, small sample size in the LHRHa monotherapy group prevent the definitive conclusion. Therefore, further study is necessary for the benefit of CAB in the era of upfront therapy.

Our study has limitations such as small sample size, short follow-up period, over-weighted effects of minority groups that are far from the center of the patient background of the IPTW method (Figure S4), selection biases for CAB and LH-RHa monotherapy, lack of data of testosterone levels after hormonal therapy, lack of the detailed information on post-treatment, no central review of pathological evaluation, the lack of information on treatment regimen and period of an anti-androgen agent administration, and the lack of ADT-related adverse events evaluation. However, our results suggest the limited efficacy of CAB over LH-RHa monotherapy in Japanese patients with mHNPC.

In conclusion, we observed no significant differences in oncological outcomes between CAB and LH-RHa monotherapy as initial treatments for patients with mHNPC.

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## Footnote

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**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau-20-966>). Drs. TN, Shingo H, SN, TS, SK, KM, YA, AI, NT, TH, and CO report grants from Japan Society for the Promotion of Science, during the conduct of the study. The other authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Hirosaki University school of Medicine (authorization number: 2017-089) and all hospitals approved the protocol. Informed consent was taken from all the patients.

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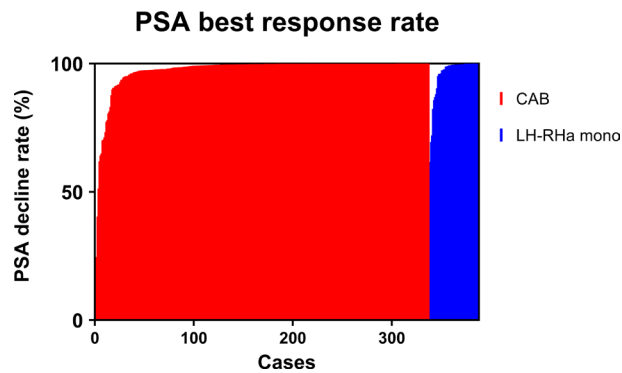
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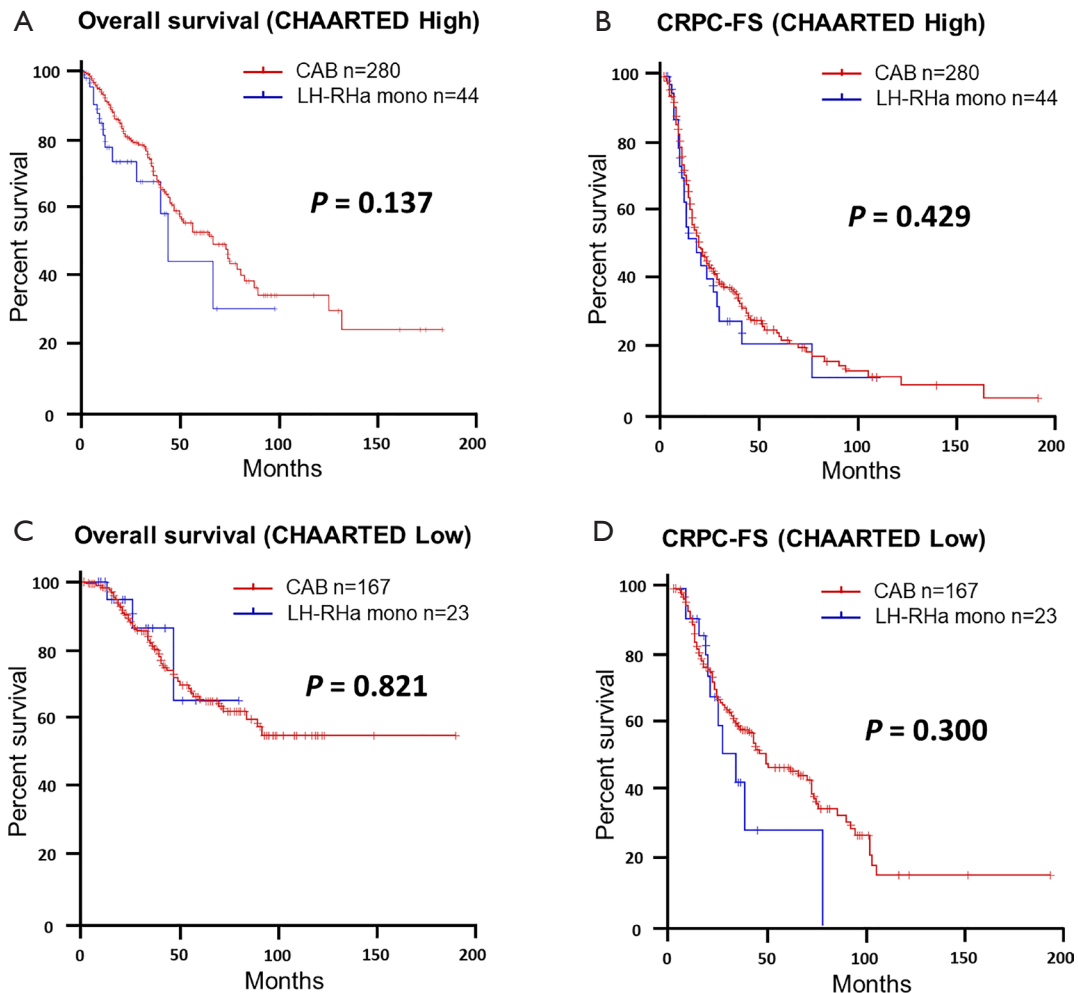


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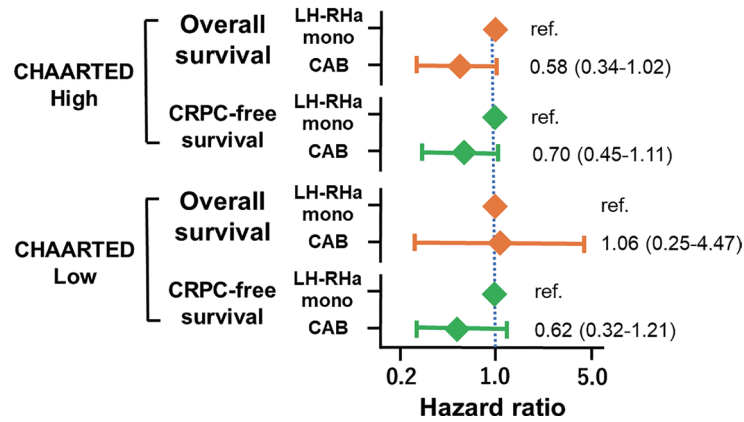


**Figure S1** PSA best response rate between combined androgen blockade therapy (CAB) and luteinizing hormone-releasing hormone analog (LH-RHa) monotherapy. Waterfall plots show the best PSA reduction rate with CAB and LH-RHa monotherapy. PSA, prostate-specific antigen.



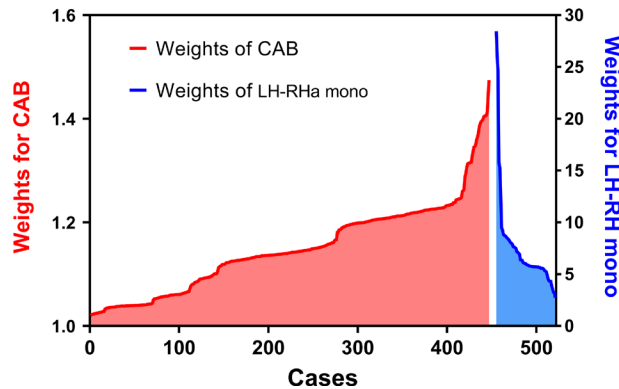
**Figure S2** Oncological outcomes between combined androgen blockade therapy (CAB) and luteinizing hormone-releasing hormone analog (LH-RHa) monotherapy by CHAARTED classification. The 5-year overall survival was compared between the CAB and LHRHa monotherapy in the CHAARTED high (A) and low (C). The 5-year CRPC-FS was compared between the CAB and LHRHa monotherapy in the CHAARTED high (B) and low (D).

### IPTW-adjusted Cox regression model



**Figure S3** Multivariate Cox hazard proportional analysis adjusted by inverse probability of treatment weighting (IPTW) model for prognosis by CHAARTED classification. IPTW-adjusted multivariate Cox hazard proportional analysis was performed to investigate the effect of combined androgen blockade on overall survival, and castrate-resistant prostate cancer free survival by CHAARTED classification. Adjusted variables were age, iPSA, ECOG-PS, GS, EOD, CHAARTED classification, treatment with DTX, AA and/or ENZ, estramustine, BMA. iPSA, initial prostate-specific antigen; ECOG-PS, Eastern Cooperative Oncology Group performance status; GS, Gleason score; EOD, extent of disease; DTX, docetaxel; AA, abiraterone acetate; ENZ, enzalutamide; BMA, bone-modifying agents.

### Weighting by the inverse probability of treatment



**Figure S4** Weighting by the inverse probability of treatment of combined androgen blockade therapy (CAB) and luteinizing hormone-releasing hormone analog (LH-RHa) monotherapy. The weight for treatment between the CAB and LH-RHa monotherapy groups were shown.