Efficacy of Combined Androgen Blockade with Zoledronic Acid Treatment in Prostate Cancer with Bone Metastasis: The ZABTON-PC (Zoledronic Acid/Androgen Blockade Trial on Prostate Cancer) Study

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Abstract. *Aim: Zoledronic acid (ZA) reduces the risk of skeletal-related events (SREs) in castration-resistant prostate cancer (CRPC) with bone metastasis and improves quality of life. It remains unclear when clinicians should initiate ZA treatment. Patients and Methods: Hormone-naïve patients were randomized to a combined androgen blockade (CAB) group or CAB with ZA group (CAB-ZA) based on Gleason score (GS) or extent of disease. The primary end-point of the study was progression-free survival (PFS) and the secondary end-point was incidence of SREs and bone pain. Results: Thirty-one and 29 patients among 60 enrolled patients were assigned to the CAB group and the CAB-ZA group, respectively. There was no significant difference in PFS between the two groups. Subgroup analyses revealed better PFS in the CAB-ZA group with GS ≥8 (p=0.021). Moreover, incidence of SREs, including bone pain, was lower in the CAB-ZA group (p=0.019). Conclusion: CAB-ZA treatment was found to improve PFS for patients with prostate cancer with high GS. CAB-ZA treatment could be recommended for treatment of patients with prostate cancer.*

The standard treatment strategy against prostate cancer (PC) with bone metastasis is androgen ablation. Currently, combined androgen blockade (CAB) using bicalutamide in combination with luteinizing hormone-releasing hormone (LH-RH) agonist as castration means is performed widely in Japan, since a significant overall survival advantage has been recognized in favor of CAB over LH-RH agonist monotherapy (1). Furthermore, an alternative anti-androgen therapy in which bicalutamide is switched to flutamide after relapse is often adopted in Japan (2, 3). Since more than 90% of PC patients with bone metastasis exhibit a response to CAB, prolonged survival is anticipated with CAB. It is, therefore, extremely important to manage bone metastasis, since it causes not only bone pain but also skeletal-related events (SREs) that worsen, often markedly, the quality of life (QOL) of the patients (4, 5).

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Saad demonstrated that zoledronic acid (ZA) is the first-generation bisphosphonate enabling for better control of bone pain and reducing the incidence of SREs predominantly associated with the osteoblastic bone lesions characteristic of PC (6). In particular, it was reported that ZA administered every three weeks prolonged the median time to the first onset of SREs by 167 days compared with a placebo in patients with castration-resistant prostate cancer (CRPC) (7). In addition, in patients with renal cell carcinoma, ZA significantly prolonged the time to the first onset of SREs and significantly reduced the total risk of onset of SREs (8). Moreover, ZA tended to prolong the overall survival in patients with CRPC, although no significant difference was observed (7). Lipton *et al*. also demonstrated that bone resorption marker normalization by ZA was correlated with survival improvement in patients with solid cancer with bone metastases (9).

However, all the prospective clinical studies conducted using ZA, thus far, targeted CRPC or prevention of bone metastases of PC (10); when should clinicians actually start ZA treatment in patients with advanced PC with bone metastasis, or which type of patients with PC can benefit from the ZA treatment in terms of progression is still controversial. Since our previous *in vitro* studies demonstrated that a third-generation bisphosphonate, minodronate, not only reduced the number of osteoclasts in the tibia of a severe combined immunodeficiency mouse inoculated with human PC cells, but also had an antitumor effect and inhibited bone invasion (11, 12), it was expected that early administration of ZA to patients with PC with bone metastases might prevent relapse of PC and improve progression-free survival (PFS). Thus, in this study, we investigated whether the ZA treatment added to CAB could improve PFS in patients with advanced PC with bone metastases and whether ZA treatment could delay the onset of SREs.

Patients and Methods

Study design. This study was under a still ongoing randomized multicenter collaborative open-labeled project of CAB alone compared with CAB plus ZA in patients with stage D2 prostate cancer and registered as a clinical trial in University hospital Medical information Network (UMIN) Center in Japan (UMIN000001137). A total of 12 domestic medical institutions, including those related to Kanazawa University Hospital, participated in this study. Patients were screened at each institution after verification of eligibility criteria, and they were randomly assigned. In this prospective study, written consent to participate was obtained from all the target patients, and all the tests and examinations were performed under the approval of the Institutional Review Board (IRB) of each medical institution. Medical records of each patient were collected and analyzed statistically at the central institution.

The enrolled patients were untreated patients with PC of stage D2 in whom PC was diagnosed pathologically by prostate gland needle biopsy in the period from July 2006 to June 2011 and the presence of bone metastasis was confirmed by bone scintigraphy. Those patients who consulted the Department of Dentistry or Oral Surgery and received or were to receive an invasive dental treatment such as tooth extraction or implant within six months before participating in this study were excluded. Before participating in this study, it was confirmed that each patient maintained sufficient functions of the liver, kidney and bone marrow and had a favorable Eastern Cooperative Oncology Group (ECOG) performance status (PS) in systemic evaluations, including hematological examinations. As the first hormonal therapy, CAB was adopted, and 80 mg of bicalutamide were orally administered once a day in addition to administration of an LH-RH agonist as internal castration. The enrolled patients were randomly assigned to two groups: one group of CAB alone in which patients were treated with LH-RH agonist and bicalutamide; and one group of CAB-ZA in which patients were treated with ZA in combination with CAB, based on the baseline Gleason score (less than 7 or not less than 7), or extent of disease (EOD) score (less than 2 or not less than 2) (13). In the CAB-ZA group, 4 mg of ZA were administered by intravenous infusion within one month after starting the CAB therapy and thereafter the intravenous infusion was repeated every four weeks. In this study, 31 patients were finally registered in the group of CAB-alone and 29 in the group of CAB-ZA.

Clinical and pathological evaluations. The clinical stage was assessed by digital rectal examination (DRE), transrectal ultrasonography (TRUS), computed tomography (CT) and bone scintigraphy. The expanse of bone lesion was evaluated with the findings in bone scintigraphy according to the EOD classification. It is desirable that a central pathologist performs the histopathological evaluation by prostate gland needle biopsy (Gleason score) at a single medical institution, since the Gleason score is one of the most important factors for the evaluation of the therapeutic effect and prediction of prognosis, and the evaluation results may differ from pathologist to pathologist. In this study, however, the Gleason score was determined at each medical institution by a pathologist specialized in urology.

Definition of progression. When the prostate-specific antigen (PSA) level was elevated, the presence/absence of anti-androgen withdrawal effect (AWE) was first confirmed. The change of the anti-androgen therapy (including the change of the drug type) to 375 mg/day flutamide was decided upon discretion of the physician in charge at each medical institution. Progression of the disease was defined as a case where the elevation of PSA level was confirmed at three consecutive time points (in three consecutive months). However, the elevation of PSA level after a transient decrease of PSA level in the following cases was not to be judged as progression: (i) cases where bicalutamide was withdrawn and AWE was confirmed with a decrease of the PSA level, and (ii) cases where bicalutamide was switched to 375 mg/day flutamide and the PSA level decreased once. In other words, the non-progression period was defined as the period from the day of treatment start to the time point of initiation of elevation of PSA level, before the treatment with estramustine phosphate or docetaxel.

End-points. In this study, the primary end-point was PSA progression-free survival (PFS), and the secondary end-points were incidence of SREs and bone pain and causal relationship between the ZA treatment and the change of bone turnover markers. In

Table I. *Baseline patient characteristics*.

Characteristic	CAB alone (n=31)	(%)	CAB-ZA (n=29)	(%)	*p*-Value
Observation (months)					
Average	27.4		32.1		
Age (years)					
Median	71.8		71.7		0.99
Range	50.2-83.1		46.7-86.4		
PS					
0	19	(61)	19	(66)	
1	10	(32)	8	(28)	0.77
2	2	(6)	2	(7)	
EOD score					
1	14	(45)	13	(45)	
2	8	(26)	5	(17)	0.75
3	7	(23)	9	(31)	
4	2	(6)	2	(7)	
Initial PSA (ng/ml)					
Median	366.9		399		0.59
Range	46.4-4526.8		34.2-7410.0		
Gleason sum					
7	7	(23)	3	(10)	0.37
8	9	(29)	10	(35)	
9	13	(42)	15	(52)	
10	2	(6)	1	(3)	

Performance status (PS), extent of disease (EOD), and prostate-specific antigen (PSA).

general, SREs are often assessed with four items as follows: (i) pathological fracture, (ii) spinal cord compression, (iii) radiotherapy to the bone lesion, and (iv) surgical operation of bone lesions, or with five items including additionally (v) hypercalcemia. Moreover, the appearance of bone pain was also included in the assessment in this study.

Statistical analyses. The differences in variables related to patient background and bone turnover markers were evaluated using the Mann-Whitney *U*-test. The rate of PFS was estimated by the Kaplan-Meier method. Two-sided *p*-values were calculated in all tests, and the differences were evaluated by log-rank test. In this study, differences of $p \leq 0.05$ were considered significant. For statistical analyses, the GraphPad Prism® version 5.0 (GraphPad Software Inc., San Diego, CA) was used.

Results

Table I shows the patients' background. The mean age was 71.8 years in the CAB-alone group and 71.7 years in the CAB-ZA group. The mean observation period was 27.4 months in the CAB-alone group and 32.1 months in the CAB-ZA group. There were no statistically significant differences between the two groups in age, PS, EOD score at the start of study, PSA level at biopsy, and Gleason score obtained from the biopsy sample. Out of the 60 included patients, 31 were randomly assigned to the CAB-alone arm, and 29 to the CAB-ZA arm (Table I). In patients, disease was controlled with CAB alone, while in the CAB-ZA group, disease in 18 patients was controlled. In total, 14 patients had died from PC during the observation period, eight in the CAB-alone group and 6 in the CAB-ZA group, respectively (Figure 1). Figure 2A shows the total rate of PFS in each group. In the observation period up to the present time point, no significant difference was recognized between the two groups. However, a tendency for better PFS of the CAB-ZA group than that of the CAB-alone group was found. Figure 2B shows the results of subgroup analysis in the patients whose baseline EOD score was at least 2. No statistically significant difference was seen again between the two groups ($p=0.158$), but the time to 50% PFS was prolonged in the CAB-ZA group. Furthermore, Figure 1C shows the results of subgroup analysis in the patients whose baseline Gleason score was at least 8. The time to 50% PFS was significantly prolonged in the CAB-ZA group ($p=0.021$), and the prolonged time reached 11 months compared with the CAB-alone group.

Next, the SREs and bone pain were also evaluated (Figure 3). In the observation period up to the present time point, 11 patients experienced bone pain in the CAB-alone group and seven in the CAB-ZA group. The time to the first appearance of bone pain was 11.7 months in the CAB-alone group and 17.2 months in the CAB-ZA group, suggesting that co-administration of ZA might be able to delay the appearance of

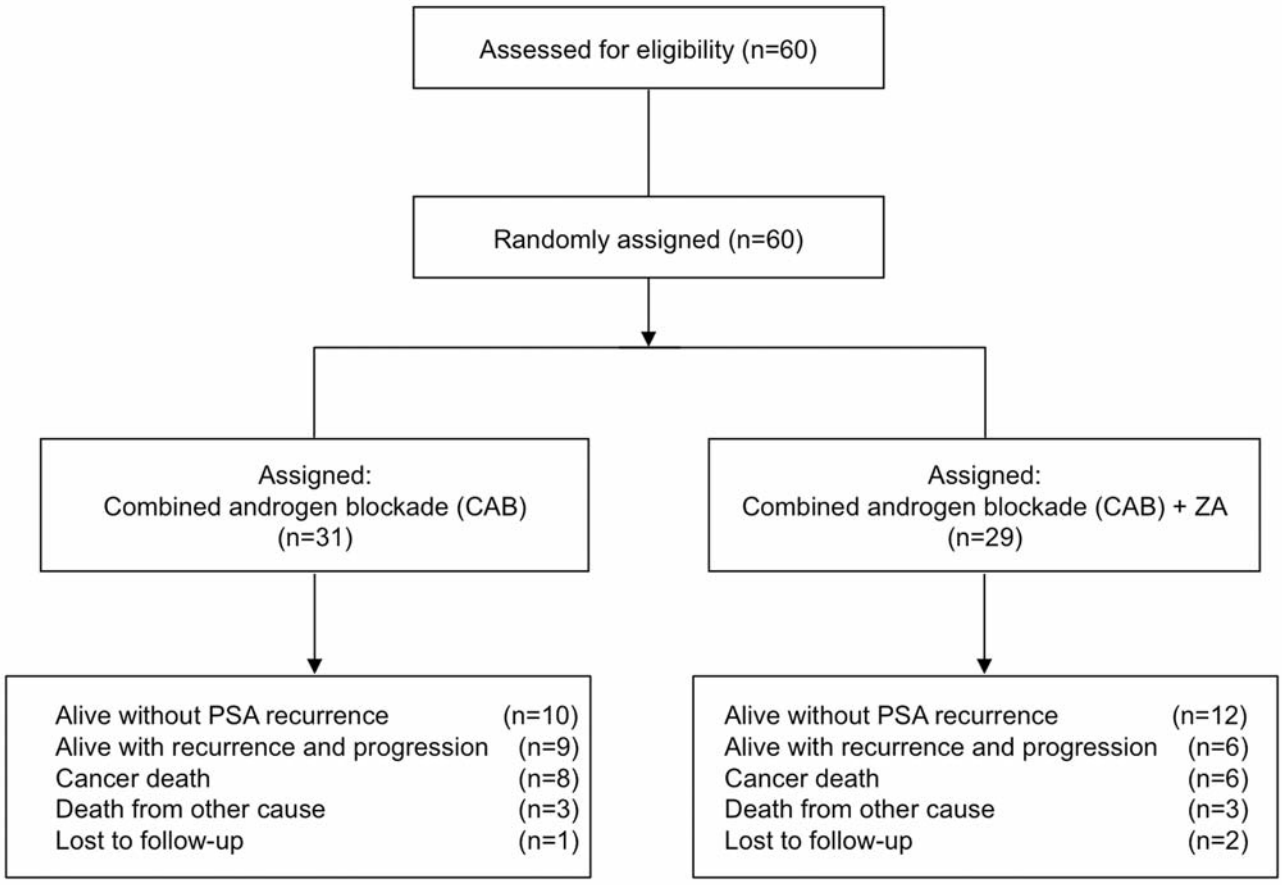


Figure 1. *Study design and patient allocation. Prostate-specific antigen (PSA), Zoledronic acid (ZA).*

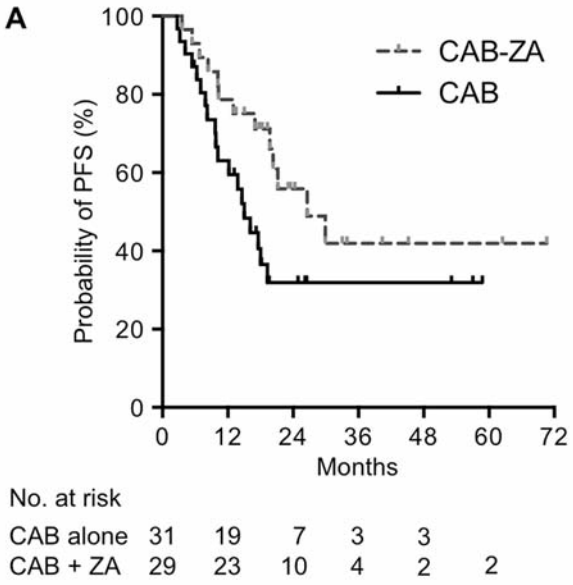
bone pain (Figure 3A). In the CAB-ZA group, the patients experiencing bone pain were generally well-controlled with oral Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or opioids. In the CAB-alone group, pathological fractures and spinal cord compression were observed in three patients. The affected patients received external-beam radiation therapy (EBRT) or surgical treatment. Figure 3B shows the incidence of SREs. Statistically significant differences were recognized between the two groups, and it was shown that the occurrence of SREs, including bone pain was delayed by continued co-administration of ZA.

During the observation period, there were no serious adverse events, such as osteonecrosis of the jaw and serum hypocalcium. But for two patients in the CAB group, ZA was additionally used for reduction of bone mineral density after long-term hormonal treatment.

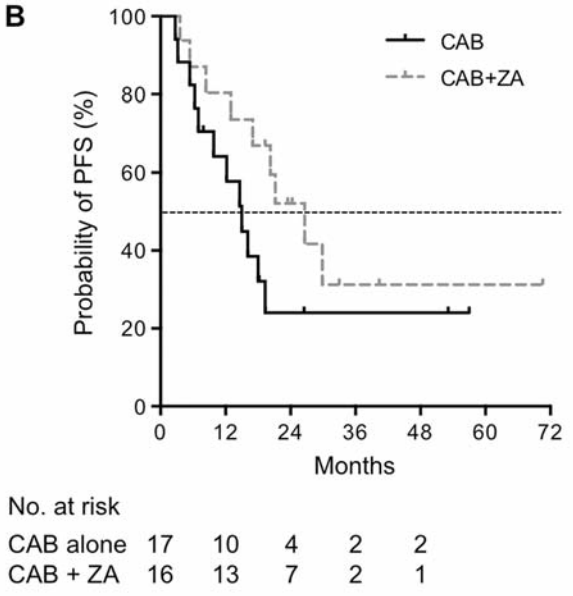
In terms of the baseline level of the bone resorption marker, C-terminal crosslinking telopeptide of type I collagen (1-CTP), and the bone formation marker, bone alkaline phosphatase (BAP), the patients of each group were divided into two groups, for subgroup analysis of PFS between the CAB-alone group and the CAB-ZA group. The subgroup analysis was performed only with these baseline values (Kaplan–Meier plots not shown). There were no significant differences in subgroup analysis. However, it was shown that early coadministration of ZA would be more useful in patients with more advanced disease or higher risk at the start of CAB treatment, such as patients with a higher PSA level, a higher EOD score, a higher Gleason score (not less than 8) or a higher value of bone turnover marker (Figure 4).

Discussion

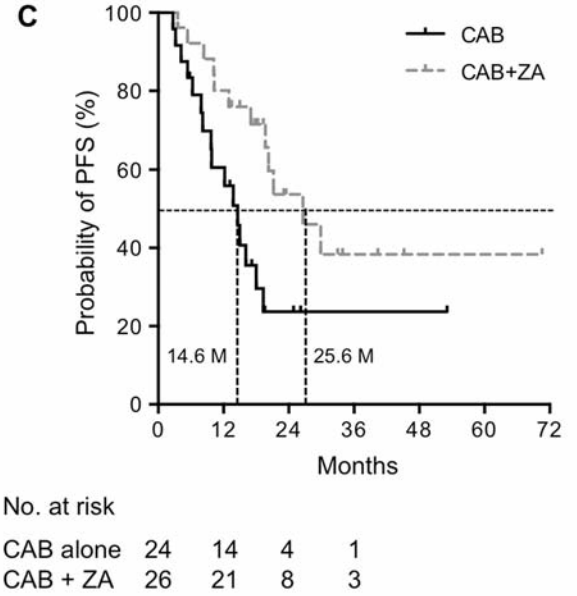
ZA is said to produce a significant delay in the occurrence of SREs and to improve bone pain in patients with CRPC with bone metastasis, and it has been also reported that co-administration of docetaxel and ZA could be promising against CRPC with bone metastasis (14). However, previous studies on when clinicians should start the treatment with ZA or which type of patients should be administered ZA earlier



	p-Value (log-rank)	HR (95% CI)
CAB alone		1.907
CAB-ZA	0.073	(0.941 – 3.865)



	N	*p*-Value (log-rank)	HR (95% CI)
CAB alone	17		0.564
CAB-ZA	16	0.158	(0.143-0.98)



	N	*p*-Value (log-rank)	HR (95% CI)
CAB alone	24		0.548
CAB-ZA	26	0.021	(0.076 – 1.022)

Figure 2. *Kaplan–Meier plots of rate of progression-free survival. (A) All the patients. (B) Subgroup analysis of the patients whose baseline EOD score was ≥2. (C) Subgroup analysis of the patients whose baseline Gleason score was ≥8. Combined androgen blockade (CAB), prostatic specific antigen (PSA), zoledronic acid (ZA).*

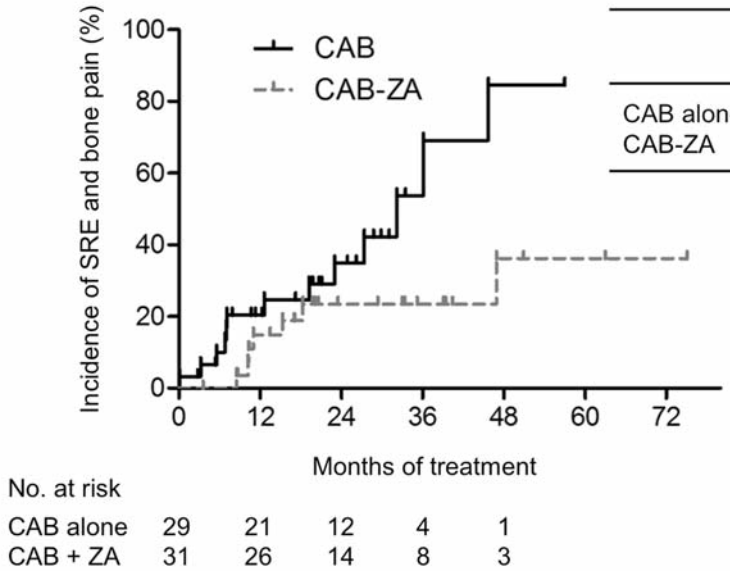
were limited to retrospective analyses, involving comparisons with the historical control, and no prospective studies have been conducted so far (15, 16). The results of the present study may help to resolve the issue of when clinicians should start the treatment with ZA in patients with advanced PC with bone metastasis.

In the present study, all the patients administered ZA from the beginning of CAB therapy exhibited prolongation of PFS,

A

	CAB alone (n=31)	CAB + ZA (n=29)				CAB alone	CAB +ZA
Event			Duration (average, month)		Treatment		
Bone pain	11	7	11.7	17.2	Medicine	10	6
					EBRT	1	3
					Strontium	2	
					Zoledronic acid	4	
Pathologic fracture	1		6.8		EBRT	2	
Spinal cord compression	2		9.2		Bone surgery + EBRT	1	

B



		p-Value (log-rank test)	HR (95% CI)
CAB alone	31		0.3812
CAB-ZA	29	0.019	(0.154 – 0.943)

No. at risk					
CAB alone	29	21	12	4	1
CAB + ZA	31	26	14	8	3

Figure 3. *Summary of SREs and bone pain (A) and Kaplan–Meier plots of incidence of SREs and bone pain (B). Prostatic specific antigen (PSA), Zoledronic acid (ZA), external-beam radiation therapy (EBRT).*

although no significant difference was recognized. However, PFS was significantly improved in the patients with high malignancy (baseline Gleason score of ≥8). This fact suggests that ZA might not only have an apoptosis-inducing effect on osteoclasts but an antitumor effect as well (12, 17, 18). In addition, clinically, we reported that the bisphosphonate, suppressed serum PSA level in patients with CRPC with bone metastasis and that ZA improved not only bone metastasis but also lung metastasis and liver metastasis of kidney cancer (19, 20). Furthermore, in patients with breast cancer without bone metastasis, an antitumor effect of ZA was reported (21, 22).

The reason why no significant differences in PFS of the patients overall were not significant but the differences in PFS of the patients with GS ≥8 between two groups may be that CAB monotherapy can control the cancer to a certain extent in patients with tumor of low malignancy but additional ZA treatment is necessary in those with highly malignant tumors. As a result, co-administration of ZA might improve the PFS of patients with GS ≥8.

One of the most prominent effects seen upon ZA treatment in patients with cancer is improvement of bone pain. It was reported that ZA also improves bone pain in

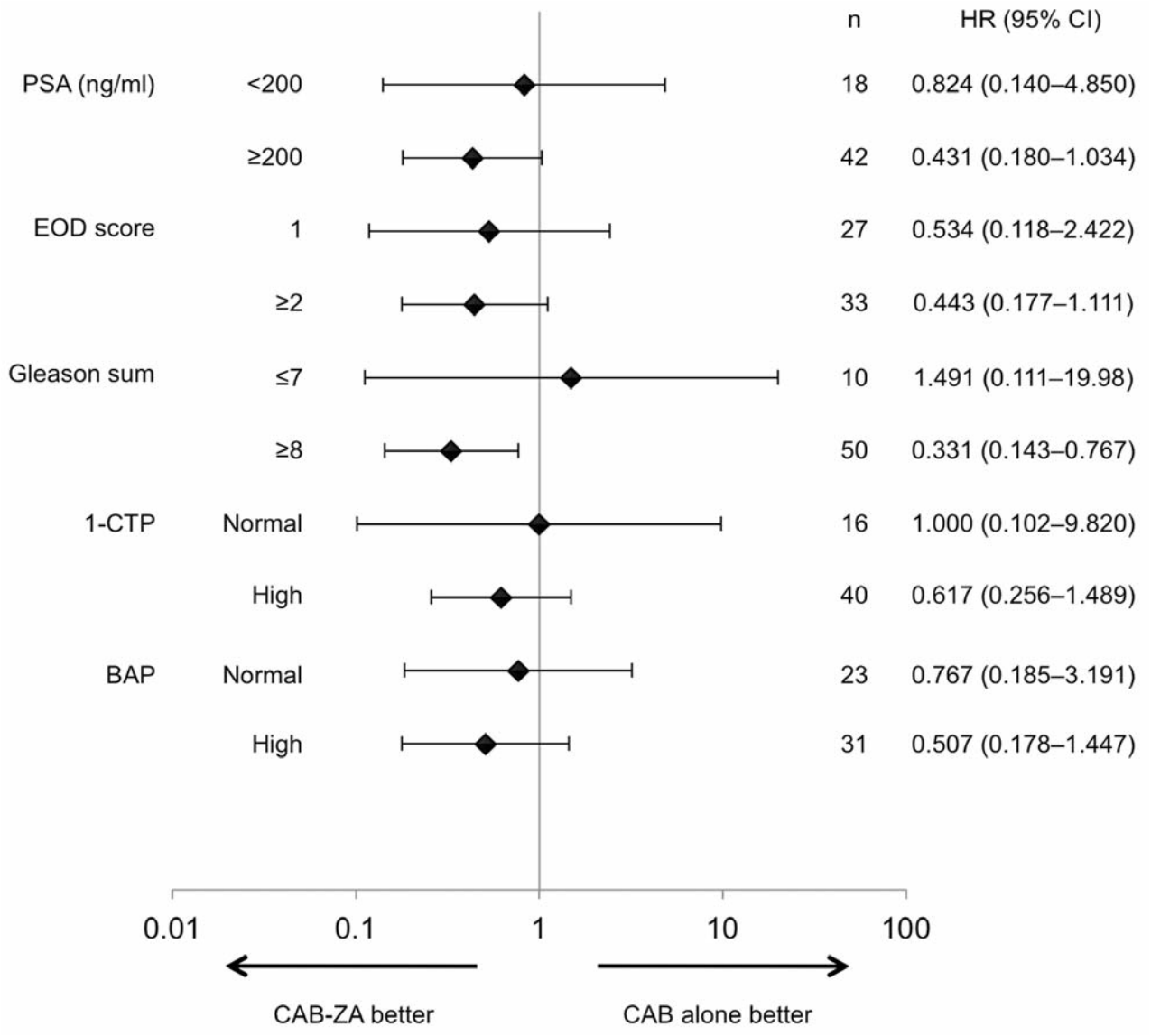


Figure 4. *Subgroup analyses of hazard ratio for PFS regarding PSA, EOD score, GS, 1-CTP, and BAP.*

patients with PC, breast cancer, and multiple myeloma with bone metastasis (23). Continuous co-administration of ZA from an early stage of treatment delayed the occurrence of bone pain and generally prevented severe SREs, such as pathological fractures and spinal cord compression in this study. Furthermore, statistically significant differences were recognized in the incidence of SREs, including bone pain. This study also showed that early co-administration of ZA would be more beneficial in patients with more advanced disease or a higher risk at the start of CAB treatment, such as patients with a higher PSA level, a higher EOD score, a higher Gleason score or a higher value of bone turnover marker, in terms of the SRE-free rate.

In conclusion, since ZA had not only a preventive effect on the occurrence of SREs but also a progression-delaying effect, probably due to a direct antitumor effect, in the treatment of PC with bone metastasis, the use of ZA from the beginning of hormonal therapy is recommended, even in the absence of bone pain, at least in patients with a high Gleason score. However, careful observation of the patient's progress is essential, since the long-term use of ZA may increase the incidence of adverse effects, such as osteonecrosis of the jaw, renal dysfunction, and hypocalcemia.

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