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Apalutamide in Patients with High Burden of Metastatic Hormone-sensitive Prostate Cancer: A Subgroup Analysis of TITAN

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Abstract

Background and objective: A post hoc analysis of TITAN evaluated the clinical benefit of apalutamide plus androgen-deprivation therapy (ADT) versus ADT alone in metastatic hormone-sensitive prostate cancer (mHSPC) with high disease burden.

Methods: Patients were assessed in subgroups of those with four to fewer than ten, ten to <20, or ≥20 bone metastases; with lung but not liver metastases; and with no/mild or moderate/severe pain at baseline. Prostate-specific antigen (PSA) response, overall survival (OS), other endpoints, and safety were assessed using descriptive statistics, Kaplan-Meier method, and Cox proportional hazard model.

Key findings and limitations: Higher proportions of patients receiving apalutamide than those receiving placebo achieved a deep PSA response of ≤0.2 ng/ml at 3, 6, and 12 mo of treatment initiation regardless of the disease burden. OS benefit favored apalutamide plus ADT versus ADT alone in all bone metastasis subgroups: four to fewer than ten (hazard ratio [HR]: 0.68 [95% confidence interval 0.44–1.03]; $p = 0.07$), ten to <20 (0.61 [0.37–1.00]; $p = 0.048$), or ≥20 (0.53 [0.39–0.72]; $p < 0.001$) bone metastases. Addition of apalutamide to ADT was beneficial across other endpoints and in patients with lung but no liver metastases and regardless of pain at baseline. No new safety signals were observed across subgroups.

Conclusions and clinical implications: These findings provide strong evidence for early intensification with apalutamide plus ADT in patients with mHSPC regardless of the disease burden.

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ADVANCING PRACTICE

What does this study add?

Triple regimens of androgen receptor pathway inhibitors (ARPIs) with androgen-deprivation therapy (ADT) and docetaxel are recommended mostly for high-volume metastatic hormone-sensitive prostate cancer (mHSPC), but expose patients to docetaxel-associated toxicity. This post hoc analysis of the TITAN study demonstrates that patients with a large number of bone metastases, even those with ≥ 20 bone lesions, derived the benefit of prolonged survival, deep and rapid prostate-specific antigen response, and delayed onset of castration resistance from treatment with apalutamide plus ADT. Consistent benefit was also observed among patients with other factors associated with high disease burden such as lung but not liver metastases and pain at baseline. These findings strongly support treatment intensification with doublet apalutamide and ADT for patients with high-burden mHSPC.

Clinical Relevance

Addition of ARPI to ADT for the treatment of mHSPC has been associated with significant benefits in patients with low- and high-volume disease; however, some specific subgroups such as patients with high and very high burden of disease had not been previously analyzed. This post-hoc analysis of the TITAN study assessed the benefit of intensifying treatment with apalutamide in patients with high-burden disease and found a positive impact on survival in patients with large numbers of bone metastases and in patients with pain at baseline, and a positive trend for patients with metastases in lung but not liver. These results further support treatment intensification with apalutamide in patients even with high- and very high-burden disease. Associate Editor: Elena Castro.

Patient Summary

We compared the benefit of adding apalutamide to ADT for patients with mHSPC and a high number of metastases, lung metastases, or pain at baseline. We found that apalutamide plus ADT prolonged patient survival versus ADT alone regardless of the metastasis number, location in the lungs, or pain.

1. Introduction

Metastatic hormone-sensitive prostate cancer (mHSPC) is characterized by cancer spreading beyond the prostate while still responding to androgen-deprivation therapy (ADT) [1]; mHSPC is a complex and heterogeneous disease, with the number, location, and timing of metastases impacting prognosis and treatment strategies [2–4]. High disease burden in mHSPC potentially reflects more aggressive disease [5].

There is no consistent or validated definition of high burden in mHSPC. The most commonly used definition is high-volume disease based on the number and location of metastases, as per the CHAARTED clinical trial: any visceral metastases or four or more bone metastases, with one or more being outside of the pelvis and spine [6]. High-burden disease, defined as polymetastases in the bones or visceral organs and high-volume disease with synchronous presentation, indeed confers poor prognosis in mHSPC [6–12]. However, thresholds quantifying high-volume/polymetastatic or low-volume/oligometastatic disease vary between studies [6,13,14]. Moreover, the high-volume CHAARTED classification includes patients with very different intrinsic vital prognostic characteristics (eg, four or five versus more than ten or >20 bone metastases, presence/absence of visceral metastases or synchronous/metachronous metastases [8,12,15,16]). The cutoff point of four bone metastases is arbitrary because it has been shown that the

unfavorable prognosis is a continuous variable in relation to the number of bone metastases: the greater the number of lesions, the worse the probable cancer-specific survival [17]. Additionally, liver and lung metastases, although usually reported together in clinical trials, have been associated with divergent survival outcomes: liver metastases with poorer survival and lung metastases with the same outcome as bone-only disease [2,11]. Regardless of the metastasis volume, pain is also an unfavorable prognostic factor [18]. Given the heterogeneity of patients included in the high-volume group, with many factors contributing to disease burden and impacting prognostic outcomes, clear criteria for patient selection and individualized treatments are needed urgently.

Combination therapies of ADT plus an androgen receptor pathway inhibitor (ARPI), such as abiraterone acetate plus prednisone, enzalutamide, and apalutamide, are the standards of care for mHSPC [3]. These have demonstrated survival benefit in the overall patient population and in subgroups with different disease volumes [19–22].

For patients with high-volume mHSPC, interest is rising in triplet regimens that combine ARPIs, ADT, and docetaxel, driven by improved outcomes when abiraterone acetate plus prednisone or darolutamide was added to docetaxel and ADT in phase 3 studies [23–25]. Based on these studies, the American Society of Clinical Oncology and European Association of Urology guidelines also recommend triplet therapy for high-volume and synchronous mHSPC [3,26],

and 54% of Advanced Prostate Cancer Consensus Conference 2024 panelists voted for these regimens for patients with high-volume mHSPC who are chemotherapy fit [4]. However, the added value of docetaxel to that of ARPI doublet therapy is unknown because no clinical trial has compared ARPI doublet therapy with ARPI triplet therapy. The First US Prostate Cancer Conference experts agreed that not all patients should receive triplet therapy [27]. Consequently, clinical decision-making for patients with mHSPC is complicated, indicating a clear need for careful patient selection to ensure appropriate and effective therapies while avoiding possible docetaxel-associated toxicity.

Various characteristics of the TITAN population, including anatomical locations (exact number of bone metastases and affected visceral organs) and symptoms manifested as pain at baseline, allow for a detailed examination of treatment intensification with apalutamide in different subgroups of patients with high-volume mHSPC, defined as per the CHAARTED criteria. Given the arbitrariness of the CHAARTED high-volume disease definition and the complexity of disease burden and symptoms observed in clinical practice, we present a post hoc analysis assessing whether apalutamide treatment effect is consistent in a heterogeneous population of patients from TITAN with high and very high disease burden, defined by varying numbers of bone metastases, presence of lung metastases, or pain at baseline.

2. Patients and methods

2.1. Study design and patients

TITAN was a randomized, double-blind, placebo-controlled, multinational phase 3 study investigating whether patients with mHSPC benefit from the addition of apalutamide to ADT. In total, 1052 patients with mHSPC were randomly assigned (1:1) to oral apalutamide 240 mg once daily ($n = 525$) or placebo ($n = 527$) added to continuous ADT (ie, a gonadotropin-releasing hormone analog or bilateral orchiectomy; [Supplementary Fig. 1](#)). The complete study design, primary data, and final analyses have been reported [20,21]. The coprimary endpoints were radiographic progression-free survival (rPFS) and overall survival (OS).

This post hoc analysis aimed to evaluate the effectiveness and safety of apalutamide plus ADT versus placebo plus ADT in patients with highly heterogeneous, high-burden disease. All patients had bone metastases at enrollment and were further classified into those with fewer than four, four to fewer than ten, ten to <20, or ≥ 20 baseline bone metastases, irrespective of the metastases in other locations; the presence of lung ($\pm$ other but not liver) metastases at baseline; or a Brief Pain Inventory–Short Form (BPI-SF) item 3 (worst pain) score at baseline of 0–3 (no/mild pain) or ≥ 4 (moderate/severe pain). The eligibility criteria for TITAN have been published (see the [Supplementary material](#) for a brief description) [20].

2.2. Outcomes

The endpoints evaluated in this post hoc analysis included OS, rPFS, time to prostate-specific antigen (PSA) progression and PSA response, time to castration resistance, second PFS

(PFS2), and safety. The endpoints were defined as in previous publications ([Supplementary material](#)).

2.3. Statistical analysis

All randomized patients (intent-to-treat population) were included. In line with the study objectives, clinical outcomes were analyzed in patients with four to fewer than ten, ten to <20, and ≥ 20 bone metastases. Radiographic PFS was assessed at 22.7 mo of follow-up (first interim analysis); all other clinical endpoints were assessed at 44.0 mo of follow-up (final analysis). Details of the statistical analysis can be found in the [Supplementary material](#).

3. Results

3.1. Patient characteristics

Among the 1052 TITAN participants, who were required to have one or more bone metastases, the numbers of bone metastases (regardless of other locations) at baseline were fewer than four in 358 (34%), between four and fewer than ten in 264 (25%), between ten and <20 in 146 (14%), and ≥ 20 in 284 (27%). Of all TITAN patients, 558 (53%) had bone-only metastases. The other patients had metastases in non-mutually exclusive locations, including in viscera in 128 (12%), lung or liver in 124 (12%), lung and other locations except for the liver in 99 (9.4%), and liver in 25 (2.4%) patients. Among all TITAN patients who had BPI-SF measured at baseline ($n = 1015$), 799 (79%) and 216 (21%) patients had BPI-SF pain scores of 0–3 (no/mild pain) and ≥ 4 (moderate/severe pain), respectively.

Baseline demographics of the included patients were generally similar regardless of treatment ([Table 1](#)); however, as expected, patients with more bone metastases had poorer performance status, higher pain and Gleason scores, high-volume disease as per the modified CHAARTED criteria [9], higher PSA levels, and more metastases in other anatomical locations than patients with fewer bone metastases ([Table 1](#) and [Supplementary Table 1](#)). Patients with lung but not liver metastases also had disease characteristics similar to those in subgroups with a high number of bone metastases ([Supplementary Table 1](#)).

3.2. Clinical outcomes

A higher proportion of apalutamide-treated than placebo-treated patients achieved a PSA response, regardless of the number of metastases ([Fig. 1](#)). A deep PSA response of ≤ 0.2 ng/ml at landmark 3 mo after treatment initiation was achieved in 58%, 36%, and 27% of patients with four to fewer than ten, ten to <20, and ≥ 20 bone metastases treated with apalutamide versus 19%, 11%, and 11% of patients treated with placebo, respectively. The rate of achieving PSA ≤ 0.2 ng/ml decreased in both treatment groups concurrently with increased numbers of bone metastases. The relative treatment effect of apalutamide for PSA responses of $\geq 50\%$ and $\geq 90\%$ at 3 mo was similar to that observed for PSA ≤ 0.2 ng/ml ([Supplementary Fig. 2](#)). The PSA response benefit observed with the addition of apalutamide to ADT was generally sustained at 6 and

Table 1 – Patient demographics and clinical characteristics according to the number of bone metastases and treatment group

	<4 bone metastases		4–<10 bone metastases		10–<20 bone metastases		≥20 bone metastases	
	Apalutamide (n = 178)	Placebo (n = 180)	Apalutamide (n = 129)	Placebo (n = 135)	Apalutamide (n = 72)	Placebo (n = 74)	Apalutamide (n = 146)	Placebo (n = 138)
Age (yr), median (IQR)	70 (65–75)	70 (63–74)	68 (63–74)	67 (61–73)	69 (65–75)	69 (62–74)	67 (62–74)	67 (62–73)
Age group (yr), n (%)								
<65	44 (25)	52 (29)	41 (32)	49 (36)	15 (21)	24 (32)	49 (34)	57 (41)
≥65–69	45 (25)	36 (20)	31 (24)	32 (24)	22 (31)	14 (19)	38 (26)	26 (19)
≥70–74	40 (22)	51 (28)	27 (21)	26 (19)	15 (21)	20 (27)	25 (17)	27 (20)
≥75	49 (28)	41 (23)	30 (23)	28 (21)	20 (28)	16 (22)	34 (23)	28 (20)
ECOG performance status, n (%)								
0	128 (72)	139 (77)	84 (65)	93 (69)	45 (63)	44 (59)	71 (49)	72 (52)
1	50 (28)	41 ^a (23)	45 (35)	42 (31)	27 (38)	30 (41)	75 (51)	66 (48)
BPI-SF pain score, n (%)	n = 166	n = 175	n = 122	n = 130	n = 70	n = 73	n = 144	n = 135
0–3	140 (84)	142 (81)	102 (84)	102 (78)	53 (76)	61 (84)	97 (67)	102 (76)
≥4	26 (16)	33 (19)	20 (16)	28 (22)	17 (24)	12 (16)	47 (33)	33 (24)
Gleason score at diagnosis, n (%)								
≤7	74 (42)	63 (35)	44 (34)	58 (43)	17 (24)	12 (16)	39 (27)	36 (26)
>7	104 (58)	117 (65)	85 (66)	77 (57)	55 (76)	62 (84)	107 (73)	102 (74)
Metastasis presentation at diagnosis, n (%)								
Synchronous	50 (28)	32 (18)	16 (12)	13 (9.6)	9 (13)	1 (1.4)	10 (6.8)	13 (9.4)
Metachronous	120 (67)	134 (74)	103 (80)	114 (84)	59 (82)	71 (96)	129 (88)	122 (88)
Mx	8 (4.5)	14 (7.8)	10 (7.8)	8 (5.9)	4 (5.6)	2 (2.7)	7 (4.8)	3 (2.2)
Disease volume ^b , n (%)								
High volume	17 (9.6)	14 (7.8)	97 (75)	115 (85)	67 (93)	71 (96)	144 (99)	135 (98)
Low volume	161 (90)	166 (92)	32 (25)	20 (15)	5 (6.9)	3 (4.1)	2 (1.4)	3 (2.2)
Baseline PSA (ng/ml), median (IQR)	2.61 (0.54–8.82)	2.58 (0.46–7.74)	4.59 (1.00–22.8)	3.73 (0.82–20.4)	9.42 (2.33–26.1)	3.50 (0.78–13.6)	15.7 (4.71–78.5)	19.1 (2.20–77.5)
Prior docetaxel, n (%)	11 (6.2)	9 (5.0)	10 (7.8)	13 (9.6)	11 (15)	13 (18)	26 (18)	20 (14)
Extent of metastatic disease at baseline, n (%)								
Bone ± other	178 (100)	180 (100)	129 (100)	135 (100)	72 (100)	74 (100)	146 (100)	138 (100)
Bone only	119 (67)	106 (59)	72 (56)	63 (47)	27 (38)	40 (54)	71 (49)	60 (43)
Bone + lymph node ± other	47 (26)	65 (36)	47 (36)	57 (42)	39 (54)	31 (42)	66 (45)	66 (48)
Bone + visceral ± other	17 (9.6)	14 (7.8)	14 (11)	23 (17)	9 (13)	4 (5.4)	16 (11)	31 (22)
Lung ± other	14 (7.9)	13 (7.2)	13 (10)	22 (16)	6 (8.3)	4 (5.4)	14 (9.6)	25 (18)
Liver ± other	4 (2.2)	2 (1.1)	1 (0.8)	3 (2.2)	5 (6.9)	1 (1.4)	2 (1.4)	7 (5.1)
Bone + soft tissue ± other	5 (2.8)	6 (3.3)	6 (4.7)	10 (7.4)	5 (6.9)	5 (6.8)	6 (4.1)	6 (4.3)

BPI-SF = Brief Pain Inventory–Short Form; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; PSA = prostate-specific antigen.

^a Includes one patient with ECOG performance status of 2.

^b Defined as either visceral metastases with one or more bone lesions or four or more bone lesions including one outside of the vertebral column or pelvis (modified CHAARTED criteria [9]).

12 mo across all bone metastasis subgroups (Fig. 1 and Supplementary Fig. 2).

In general, the addition of apalutamide to ADT improved survival in all patient subgroups, with the magnitude of the treatment effect increasing as the number of metastases increased (Fig. 2). In the subgroup with four to fewer than ten bone metastases, median OS was not reached in apalutamide- or placebo-treated patients, but OS benefit favored apalutamide over placebo, with nominal $p = 0.07$ (hazard ratio [HR]: 0.68 [95% confidence interval {CI} 0.44–1.03]; Fig. 2A). In patients with ten to <20 bone metastases, median OS was not reached with apalutamide and was 37.6 mo with placebo; the benefit in OS also favored apalutamide, with nominal $p = 0.048$ (HR: 0.61 [95% CI 0.37–1.00]; Fig. 2B). Similarly, in patients with ≥20 bone metastases, the median OS for those receiving apalutamide and placebo was 42.9 and 25.4 mo, respectively, and apalutamide treatment effect on OS favored it over placebo, with nominal $p < 0.001$ (HR: 0.53 [95% CI 0.39–0.72]; Fig. 2C). The Kaplan-Meier analysis of OS in patients treated with apalutamide or placebo showed that the number of bone metastases is prognostic for survival. Patients with four to fewer

than ten bone metastases had the best prognosis, while those with ≥20 bone metastases had the worst prognosis, regardless of treatment (Supplementary Fig. 3).

Treatment effect of apalutamide on other endpoints was consistent with that on OS. Radiographic PFS, time to PSA progression, time to castration resistance, and PFS2 were all prolonged in apalutamide-treated patients compared with placebo-treated patients, irrespective of the number of bone metastases at baseline (nominal p values of <0.001 or <0.05; Fig. 2D–F and 3, and Supplementary Fig. 4).

In patients with lung but not liver metastases (apalutamide, $n = 42$; placebo, $n = 57$), OS favored the addition of apalutamide to ADT (HR: 0.66 [95% CI 0.37–1.20]); results for rPFS and PFS2 were similar (Fig. 4A). Although the HR indicated a favorable outcome for apalutamide-treated over placebo-treated patients, it did not attain statistical significance ($p > 0.05$) due to the small sample size or shorter follow-up period, which consequently reduced the number of events for OS, rPFS, and PFS2. The time to castration resistance and time to PSA progression favored the addition of apalutamide to ADT, with nominal $p < 0.001$ (Fig. 4A).

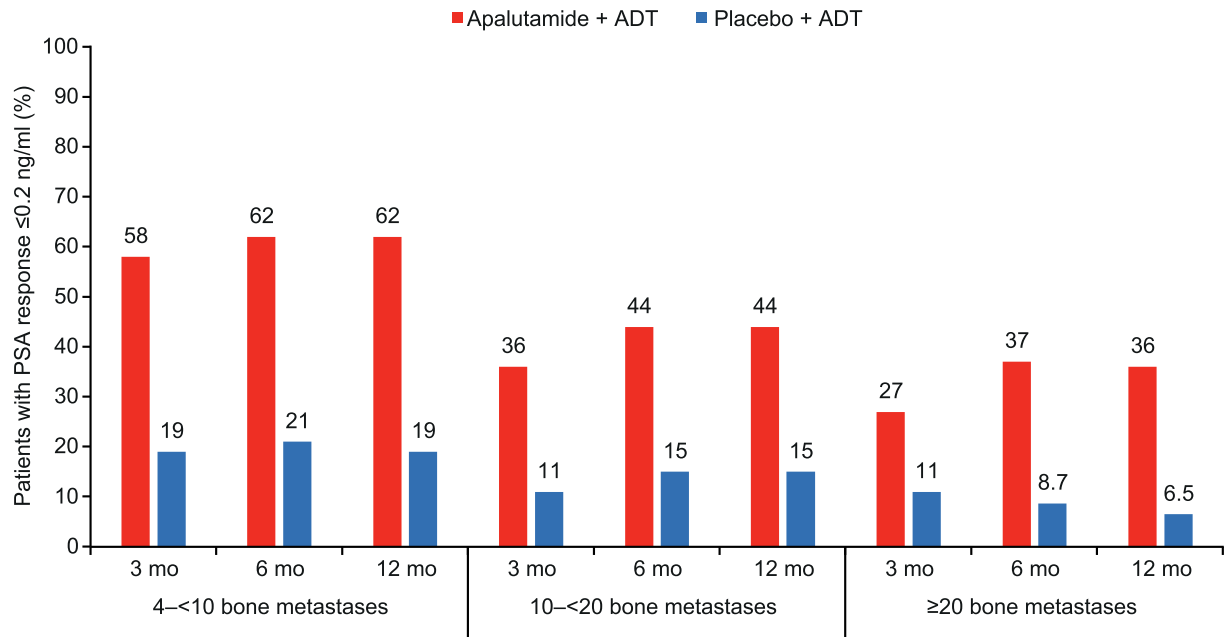


Fig. 1 – Deep PSA response ≤ 0.2 ng/ml at 3, 6, and 12 mo after treatment initiation according to the number of bone metastases at baseline. ADT = androgen-deprivation therapy; PSA = prostate-specific antigen.

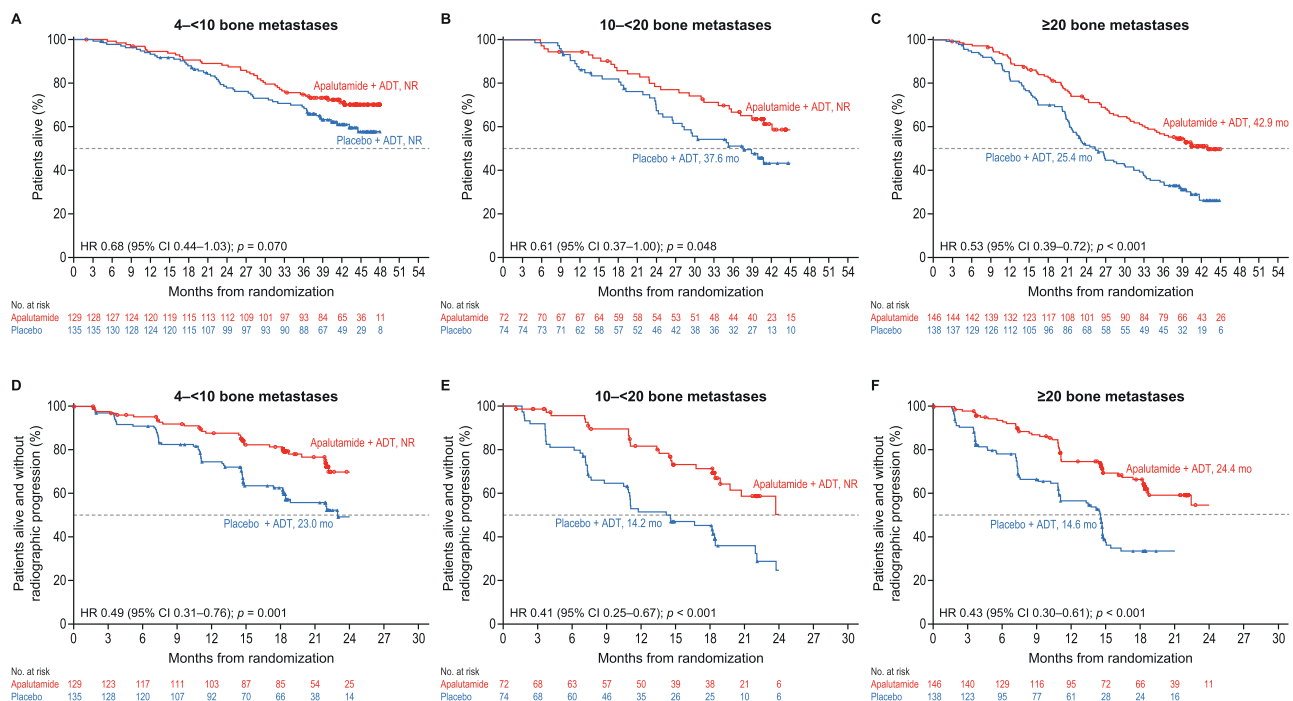


Fig. 2 – Treatment effect of apalutamide on (A–C) overall survival and (D–F) radiographic progression-free survival in patients with four to fewer than ten (A and D), ten to <20 (B and E), and ≥ 20 (C and F) bone metastases at baseline. The Kaplan-Meier curves are truncated for instances in which the number at risk in a group was < 5 . ADT = androgen-deprivation therapy; CI = confidence interval; HR = hazard ratio; NR = not reached.

Patients also derived a survival benefit from the addition of apalutamide to ADT regardless of the BPI-SF pain score at baseline (Fig. 4B). HRs for OS were 0.65 (95% CI 0.51–0.81) in patients with a BPI-SF pain score at baseline of 0–3 and 0.66 (95% CI 0.43–0.998) in those with a BPI-SF pain score

of ≥ 4 (nominal p values of < 0.001 and < 0.05 , respectively). All other assessed endpoints, that is, rPFS, time to castration resistance, time to PSA progression, and PFS2, favored apalutamide plus ADT versus placebo plus ADT regardless of the BPI-SF pain score, with nominal $p < 0.05$.

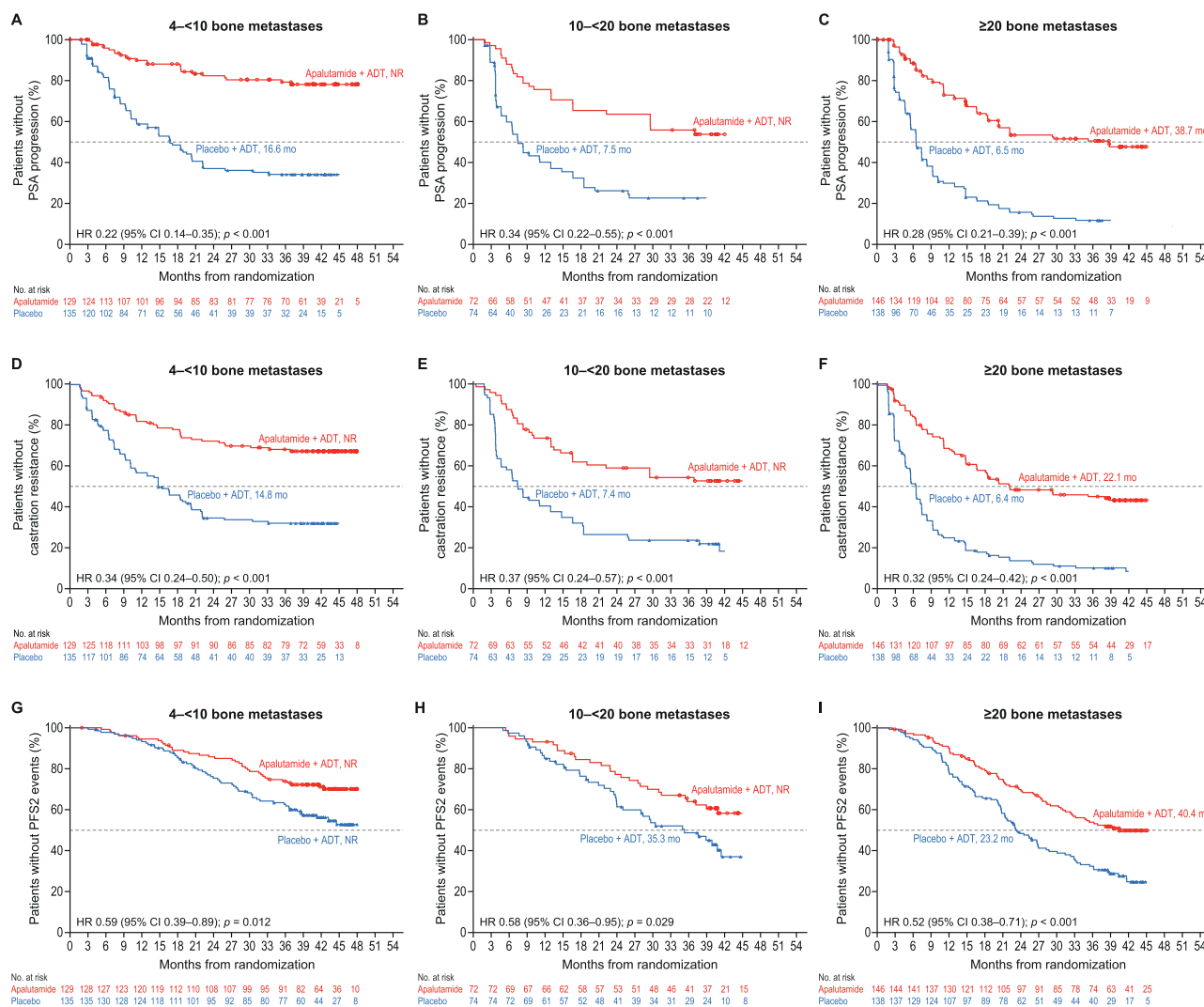


Fig. 3 – Treatment effect of apalutamide on (A–C) PSA progression, (D–F) time to castration resistance, and (G–I) PFS2 in patients with four to fewer than ten (Fig. 3A, 3D, and 3G), ten to <20 (Fig. 3B, 3E, and 3H), and ≥ 20 (Fig. 3C, 3F, and 3I) bone metastases at baseline. The Kaplan-Meier curves are truncated for instances in which the number at risk in a group was <5 . ADT = androgen-deprivation therapy; CI = confidence interval; HR = hazard ratio; NR = not reached; PFS2 = second progression-free survival; PSA = prostate-specific antigen.

3.3. Safety

Apalutamide in all patient subgroups with four or more metastases at baseline was generally well tolerated, with a safety profile similar to that reported previously. The rate of observed treatment-emergent adverse events, including any, grade 3–4, serious, and treatment-emergent adverse events of interest, was similar regardless of the number of metastases at baseline (Table 2).

4. Discussion

In this TITAN post hoc analysis, addition of apalutamide to ADT resulted in a deep and rapid PSA response and improved outcomes, such as OS and rPFS, across subgroups with various high disease burden features and unfavorable clinical factors, including high and very high numbers of bone metastases, lung $\pm$ other but not liver metastases, and moderate/severe pain at baseline. The absolute treat-

ment effect was generally maintained or even increased with apalutamide concurrently with disease burden. A small sample size in the lung but not liver metastasis subgroup limited interpretation of the results. The safety profile of apalutamide across subgroups with increased disease burden was consistent with previous reports [10,20,21].

A rapid, deep, and durable PSA response with apalutamide was previously shown in the TITAN study. Addition of apalutamide to ADT also resulted in a rapid, deep, and sustained PSA response across all subgroups, even in patients with ≥ 20 bone metastases. The number of patients who achieved a deep PSA decline from baseline to ≤ 0.2 ng/ml or a PSA decline of $\geq 90\%$ or 50% at 3 mo of apalutamide plus ADT treatment, and maintained it at 6 and 12 mo, was more than that of patients receiving ADT alone. Addition of apalutamide to ADT also improved long-term survival across all the subgroups analyzed; patients with ≥ 20 bone metastases (HR: 0.53) had greater clinical benefit than subgroups with fewer metastases (HR: 0.68 for four to fewer

A. Outcomes for patients with lung but not liver metastases

Outcomes	Events/n		Median, mo			HR (95% CI)	p-value
	Apalutamide	Placebo	Apalutamide	Placebo			
OS	17/42	31/57	NR	38.7		0.66 (0.37–1.20)	0.17
rPFS	15/42	26/57	NR	21.9		0.67 (0.35–1.27)	0.22
Time to castration resistance	17/42	42/57	NR	9.2		0.37 (0.21–0.65)	<0.001
Time to PSA progression	13/42	39/57	NR	9.2		0.31 (0.16–0.58)	<0.001
PFS2	17/42	31/57	NR	33.4		0.64 (0.35–1.16)	0.14

0 0.5 1 1.5
Favors apalutamide Favors placebo

B. Outcomes according to pain at baseline

Outcomes	BPI-SF score	Events/n		Median, mo			HR (95% CI)	p-value
		Apalutamide	Placebo	Apalutamide	Placebo			
OS	0–3	124/392	178/407	NR	52.2		0.65 (0.51–0.81)	<0.001
	≥4	39/110	52/106	NR	43.9		0.66 (0.43–0.998)	0.049
rPFS	0–3	102/392	175/407	NR	25.6		0.50 (0.40–0.65)	<0.001
	≥4	30/110	50/106	28.7	18.5		0.52 (0.33–0.83)	0.006
Time to castration resistance	0–3	135/392	287/407	NR	12.9		0.32 (0.26–0.40)	<0.001
	≥4	50/110	79/106	NR	9.2		0.45 (0.32–0.65)	<0.001
Time to PSA progression	0–3	98/392	266/407	NR	14.6		0.25 (0.20–0.32)	<0.001
	≥4	35/110	70/106	NR	10.1		0.35 (0.23–0.52)	<0.001
PFS2	0–3	127/392	187/407	NR	44.5		0.62 (0.49–0.77)	<0.001
	≥4	39/110	54/106	NR	38.8		0.61 (0.4–0.92)	0.017

0 0.5 1 1.5
Favors apalutamide Favors placebo

Fig. 4 – Treatment effect of apalutamide on clinical outcomes in patients with (A) metastases in the lung (± other locations but not liver) and (B) BPI-SF pain score at baseline of 0–3 and ≥4. BPI-SF = Brief Pain Inventory–Short Form; CI = confidence interval; HR = hazard ratio; NR = not reached; OS = overall survival; PFS2 = second progression-free survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival.

Table 2 – Treatment-emergent adverse events according to the number of bone metastases at baseline ^a

	4–<10 bone metastases		10–<20 bone metastases		≥20 bone metastases	
	Apalutamide (n = 129)	Placebo (n = 135)	Apalutamide (n = 72)	Placebo (n = 74)	Apalutamide (n = 146)	Placebo (n = 138)
Any TEAE	126 (98)	133 (99)	69 (96)	71 (96)	139 (95)	134 (97)
Grade 3 or 4 TEAEs	69 (53)	63 (47)	30 (42)	29 (39)	79 (54)	66 (48)
Any SAE	41 (32)	31 (23)	22 (31)	12 (16)	34 (23)	33 (24)
Any TEAE leading to discontinuation of trial intervention	11 (8.5)	6 (4.4)	9 (13)	4 (5.4)	13 (8.9)	8 (5.8)
TEAEs leading to death	2 (1.6)	5 (3.7)	2 (2.8)	2 (2.7)	8 (5.5)	6 (4.3)
TEAEs of interest						
Skin rash	49 (38)	15 (11)	21 (29)	6 (8.1)	32 (22)	5 (3.6)
Fall	12 (9.3)	11 (8.1)	5 (6.9)	2 (2.7)	12 (8.2)	3 (2.2)
Fracture	14 (11)	10 (7.4)	7 (9.7)	3 (4.1)	12 (8.2)	2 (1.4)
Ischemic heart disease	4 (3.1)	1 (0.7)	4 (5.6)	0	10 (6.8)	2 (1.4)
Ischemic cardiovascular disorder	1 (0.8)	1 (0.7)	2 (2.8)	1 (1.4)	4 (2.7)	2 (1.4)
Seizure	0	1 (0.7)	0	0	2 (1.4)	0

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
^a Shown are AEs of any cause that occurred from the time of the first dose of the trial intervention through 30 d after the last dose.

than ten and 0.61 for ten to <20 metastases) or even than the TITAN intent-to-treat population, reported earlier (HR: 0.65) [21]. The treatment effect of apalutamide was observed despite poor prognosis associated with a high number of bone metastases. A published subgroup analysis of TITAN patients treated with apalutamide plus ADT

showed that the most favorable OS was in patients with five or fewer bone-only metastases and the worst OS was in patients with more than five bone metastases plus metastases in other organs [10]. We further build on this observation, demonstrating an incrementally shorter time to death as the number of bone metastases increased; patients with

≥ 20 bone metastases had the worst prognosis of all subgroups regardless of treatment.

A high number of metastases is associated with poor outcomes [10,17]; however, clear treatment guidance based on the number of metastases is lacking, especially for very high metastasis counts [3,28]. Metastasis count, as a prognostic factor, is closely related to the terms of high or low volume, which are most commonly defined by the number of bone metastases (four or more with one or more outside of pelvis and spine) or visceral metastases in the so-called CHAARTED criteria [9]. These criteria were validated in the assessments of doublet treatment combinations with either an ARPI or docetaxel with ADT, or with triplet combinations of an ARPI, docetaxel, and ADT [6–9,24,29,30]. However, high-volume disease is very diverse, with many factors, such as the number of bone-only metastases, metastases in other anatomical locations, and synchronous or metachronous metastases, affecting outcomes. With the lack of guidance on the metastasis cutoff, we selected cutoffs of four to fewer than ten, ten to <20 , and ≥ 20 bone metastases based on the CHAARTED criteria [9] and the previously shown ten bone metastasis cutoff in TITAN [20]. These cutoffs allowed for a large population with ≥ 20 bone metastases, enabling meaningful evaluation of treatment in patients with very high metastasis counts. To our knowledge, our analysis is the only one that shows efficacy of doublet combination of an ARPI plus ADT in this population. Ali et al [17] demonstrated that bone metastasis count is a continuous variable for survival. We also observed worsening OS concurrently with the increasing number of bone metastases, supporting the continuous risk hypothesis.

In the final survival analysis of TITAN, we reported favorable OS with apalutamide in patients with visceral metastases (HR: 0.76), although the upper-bound 95% CI was >1 [21]. The latter may have been due to a low number of patients ($n = 128$) and heterogeneity of visceral metastases: liver metastases have been shown to be associated with worse OS than lung metastases [16]. Here, we found that in the subgroup with lung but not liver metastases, the treatment effect size on OS (HR: 0.66) was more favorable than that in the group with visceral metastases and similar to that in the intent-to-treat population (HR: 0.65) [21]. The other outcomes in the subgroup with lung but not liver metastases also favored apalutamide. The number of patients with liver metastases was too low ($n = 25$) for separate meaningful assessments. While these initial findings are encouraging regarding the treatment effect of apalutamide in this patient subgroup, it is important to note that these results should be validated through larger prospective studies to confirm their reliability and generalizability.

Patients with pain have been shown to have shorter OS than those without pain [18]. In our analysis, treatment effect of apalutamide was similar regardless of pain at baseline. The benefit on OS was similar across subgroups with no/mild and moderate/severe pain (HR: 0.65 and 0.66, respectively), and similar to that in the overall TITAN population. Similar results were observed for the other outcomes.

This analysis has some limitations, including the fact that it was post hoc and subgroups were not designed to

detect statistical differences, resulting in nominal p values only. Metastases were determined by conventional imaging only, and therefore the volume of disease might have been undervalued. As the TITAN study design did not include triplet therapy of apalutamide and docetaxel plus ADT, it is not possible to draw conclusions about the superiority of this regimen over doublet therapy of apalutamide plus ADT, or vice versa. We have shown that OS in TITAN patients who received docetaxel prior to apalutamide was similar to that in those who did not [21,31].

Taken together, our results indicate that early treatment intensification with apalutamide has significant antitumor efficacy in patients with mHSPC with very high disease burden or unfavorable clinical factors such as pain at baseline. These findings are consistent with those from other TITAN post hoc subgroup analyses demonstrating that patients derived benefit with apalutamide plus ADT regardless of the disease volume and timing of metastasis presentation [10,32,33]. To date, there are no publications that analyze the effectiveness of other ARPIs in these heterogeneous patient subgroups within the CHAARTED high-volume group. Our results provide valuable insights for improving treatment selection in mHSPC and minimizing toxicity from unnecessary treatments. Owing to a lack of clear guideline recommendations on doublet versus triplet treatment options, and on how to choose treatments specific to patients with lung metastases or those who are symptomatic [3], optimal treatment selection remains unclear. Furthermore, concerns about increased toxicity due to docetaxel in triplet therapies persist [34]. Our results indicate that patients with a high number of bone metastases, lung metastases, or pain at presentation can derive benefit from doublet therapy with apalutamide due to its favorable safety profile, while avoiding docetaxel-related toxicities.

5. Conclusions

In TITAN, patients with high and very high bone disease burden, lung metastases, or pain at baseline, apalutamide plus ADT resulted in long-term efficacy benefit compared with placebo plus ADT. No new safety signals were observed across subgroups with high disease burden. These findings provide strong evidence in favor of early intensification with apalutamide in patients with mHSPC and features of more aggressive and symptomatic disease.

Author contributions: Alejo Rodriguez-Vida had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition of data: Garcillan, Vidal, Lencart, Bhaumik, Mundle, Van Sanden.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Bhaumik, Van Sanden.

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Appendix A. Supplementary data

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