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Association Between Baseline Body Mass Index and Survival in Men with Metastatic Hormone Sensitive Prostate Cancer: ECOG-ACRIN CHAARTED E3805

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Abstract

Background: E3805 (CHAARTED) is a phase 3 trial demonstrating improved survival for men with metastatic hormone sensitive prostate cancer (mHSPC) randomized to treatment with docetaxel (D) and androgen deprivation therapy (ADT) vs ADT alone. We assessed the association of baseline body mass index (BMI) and metformin exposure with quality of life (QOL) and prostate cancer outcomes including survival in patients enrolled on the CHAARTED study.

Methods: We performed a post hoc exploratory analysis of the CHAARTED trial of men with mHSPC randomized to treatment with ADT with or without D between 2006 and 2012. Cox proportional hazards models and Kruskal-Wallis test were used to evaluate the association between BMI with QOL and prostate cancer outcomes, and between metformin exposure and survival.

Results: In 788 of 790 enrolled patients with prospectively recorded baseline BMI and metformin exposure status, lower BMI was not associated with survival, but was associated with high volume disease ($p<0.0001$) and poorer baseline QOL on FACT-P ($p=0.008$). Only 68 patients had prevalent metformin exposure at baseline in the CHAARTED trial. Four groups were identified: ADT+D+metformin (n=39); ADT+D (n=357); ADT+metformin (n=29); ADT alone (n=363). Baseline clinicopathologic characteristics were similar between groups. In this small exploratory multivariable analysis, metformin exposure was not associated with survival (HR 1.15; 95% CI 0.81–1.63, $p=0.44$).

Conclusions: There was no link between baseline BMI and survival, but lower baseline BMI was associated with features of greater cancer burden and poorer QOL.

Keywords

metastatic prostate cancer; chemohormonal therapy; quality of life; metabolism

Introduction

The treatment of advanced prostate cancer has been revolutionized during the past decade with the development of multiple new therapies for castration-resistant disease, and improved survival when combining androgen deprivation therapy with docetaxel or androgen signaling inhibitors for men with mHSPC [1, 2]. Population-based studies suggest that patient-specific health indicators, such as exercise and body mass index, and exposure to metformin, may be associated with prostate cancer outcomes.[3–5] These factors have been less frequently studied in prospective clinical trials and analysis of data from these trials may provide further insight into the association of these factors with prostate cancer patient outcomes.

Obesity is a patient-specific factor that can be associated with metabolic dysregulation. A BMI that is too high is associated with being overweight or obese, and is a predictor of cardiovascular disease, type 2 diabetes and hypertension[6]. Numerous studies also suggest that increased BMI is associated with poorer prostate cancer outcomes, including increased prostate cancer incidence, recurrence and mortality [4, 5, 7–9]. Greater BMI has also been associated with poorer overall QOL after treatment of clinically localized prostate cancer, including worse urinary symptoms [10–15]. Whether BMI is associated with prostate

cancer specific outcomes or QOL in men with mHSPC treated with hormonal therapy or chemohormonal therapy has not been defined.

The association between metformin use and cancer patient outcomes has also been a topic of debate for decades. Metformin is an oral anti-hyperglycemic drug commonly used to treat type 2 diabetes mellitus (DM). Evidence suggests that it may have putative antitumor activity through a variety of direct and indirect activities [16–18], including indirectly reducing cyclin D1 levels and pRb phosphorylation [19]. This reduction may cause antiproliferative and proapoptotic activities that can augment the *in vitro* and *in vivo* efficacy of selected chemotherapies. Clinical studies assessing metformin use in diabetic patients with breast, lung, and endometrial cancer demonstrate improved outcomes when compared with patients not receiving metformin [20] [21, 22]. The effect of metformin use on outcomes in men with prostate cancer remains uncertain. One recent population based study demonstrated improved survival in diabetic patients with vs without metformin exposure, while a separate cohort study of men receiving radiation for localized disease failed to find a benefit to metformin exposure in time to biochemical failure or overall survival [23, 24]. Further analyses to assess the association between metformin exposure and prostate cancer outcomes are needed.

To that end, we evaluated the association between BMI with clinically important prostate cancer outcomes, including disease burden, survival, and QOL during treatment of men with mHSPC with ADT chemohormonal therapy in the CHAARTED trial [25]. We also evaluated the association between metformin exposure at baseline and overall survival in the CHAARTED trial. Because metabolism in cancer patients is an interplay between cancer related cachexia and host related factors such as obesity, we also performed an integrated analysis linking metformin, BMI and QOL.

Materials and Methods

This multicenter, randomized, open-label, phase III NCI study (NCT00309985) led by ECOG (now part of ECOG-ACRIN) enrolled patients with mHSPC with a performance status suitable for treatment with docetaxel in addition to ADT as described previously [1]. Eligible patients were equally randomized to ADT alone versus ADT plus docetaxel chemotherapy at a dose of 75 mg/m^2 every 3 weeks for up to 6 cycles without daily prednisone. Randomization was stratified according to age (<70 years versus ≥70 years), ECOG performance status (0–1 versus 2), duration of prior adjuvant therapy with ADT, combined androgen blockade for >30 days, disease volume (high volume defined as the presence of visceral metastases or ≥4 bone metastases with ≥1 beyond the vertebral bodies and pelvis) and use of agents to prevent skeletal-related events (such as zoledronic acid or denosumab). All patients provided written informed consent prior to study entry. The primary endpoint of the study was OS, defined as time from randomization until death due to any cause. Baseline metformin use, BMI and QOL data were identified as priority data points, and data was collected prospectively at enrollment via case report forms (metformin use, yes/no; BMI in kg/m^2) or patient reported outcome survey instrument (QOL data). Specific medication use beyond metformin, including sulfonyurea and insulin use, and

comorbidity information, including diagnosis of diabetes, were not collected as metformin use specifically, rather than glycemic control, was of interest.

Statistical analyses:

Descriptive statistics were used to characterize patients at study entry. Kaplan–Meier estimates were used for event-time distributions. Cox proportional-hazard models, stratified according to the stratification factors at randomization, were used to estimate hazard ratios for time-to-event end points. Variables with $p<0.1$ in the univariable analysis were included in the multivariable models. Stratified log-rank tests were used to compare event-time distributions between groups. Categorical variables and continuous variables were compared with the use of Fisher's exact test and Kruskal-Wallis test, respectively. P values are two-sided, and confidence intervals are at the 95% level. This report represents data with a cutoff date for survival of April 2016 resulting in a median follow-up of 53.7 months.

Results

A total of 788 patients (of 790 in the primary analysis) were included in this analysis because they had data on baseline metformin exposure available for analysis (396 receiving ADT+D and 392 receiving ADT). Median follow-up was 53.7 mo for the population. In total 68 (8.6%) were receiving treatment with metformin at baseline (39 receiving ADT+D and 29 receiving ADT). Patient characteristics were generally balanced between treatment arms and metformin exposure groups, but fewer patients had ECOG 0, high burden of disease, Gleason <7 in the ADT + metformin use group than the others (Table 1). Median BMI was higher for patients on metformin (31 vs. 29; p=0.001 in patients receiving vs not-receiving metformin, respectively) (Table 1).

In the BMI analysis, baseline BMI was analyzed in clinical categories (BMI <25, 25≤BMI<30, and BMI ≥30 as normal and underweight, overweight, and obese, respectively). Baseline BMI was associated with extent of disease burden; men with low or normal BMI were more likely to have high volume disease than other groups. Specifically, 78.8%, 66.8% and 57.4% of men BMI<25, overweight, and obese men, respectively, had high volume disease (p<.0001) (Supplemental Table 1). There was no association between BMI and OS, but there was a trend towards improved survival in obese patients (Figure 1A; Table 2). Metformin exposure was included in the multivariable model because it was a prespecified exposure of interest. Although it was not included in the multivariable analysis initially because only variables with a $p<0.10$ in the univariable analysis were initially included, an analysis forcing BMI into the multivariable model despite the lack of significance in the univariable model was not significantly different from the model excluding BMI (Table 2). Response to treatment arm in these weight subgroups was assessed. In 132 patients with BMI<25, although there was no significant association between treatment arm and OS, the treatment effect was consistent with the overall and other subgroups with benefit from docetaxel (HR 0.65, 95% CI: [0.39, 1.09], p = 0.10) (Figure 1B). For 331 overweight (BMI >25 but < 30) men, there was improved OS associated with ADT+D as compared with ADT (HR 0.72, 95% CI: [0.53, 0.99], p=0.046), and for 324

obese men (BMI>30) ADT+D was associated with a consistent trend to improved OS vs ADT (HR 0.74, 95%: [0.53, 1.03], p=0.08) (Figure 1C and 1D).

We also assessed the association between baseline BMI and QOL. QOL by median FACT-P score was poorer among patients with BMI<25 (118) when compared with overweight and obese patients (125 and 123, respectively, p=0.008) (Table 3). This difference met criteria for clinically meaningful difference (≥ 6–10) between BMI <25 and overweight, but not when other groups were directly compared [26]. Median FACIT-Fatigue score was lower (increased fatigue) among patients with BMI <25 when compared with overweight patients, but was similar to obese men (44.0 vs 46.0 vs 43.3 for BMI <25 vs overweight vs obese, respectively, p=0.004 for comparison of all 3 groups), indicating greater fatigue for underweight and obese patients. However, this small difference only met criteria for minimally important difference between overweight and obese patients (change by 3–4) [27], suggesting that fatigue levels are similar for BMI <25 and overweight patients, but may be greater in obese patients. Median pain score was similar between BMI <25 and obese patients (median BPI 1.25 in both groups), but was numerically lower in overweight patients (median BPI 1.0, p=0.07). (Table 3) This difference did not meet criteria for minimally important difference (difference by 2) [28]. Baseline QOL data by treatment arm was not substantially different.

In the metformin analysis, prostate cancer was the cause of death in 15/22(68%) of ADT+D+metformin, 132/166(80%) ADT+D, 12/15(80%) ADT+metformin and 164/196(84%) ADT alone patients (Table 4). There was no significant difference in OS (Figure 2) by metformin exposure within the ADT+D treatment arm (p=0.31) and ADT alone arm (p=0.76) using the stratified logrank test (Table 4). Metformin exposure was not associated with survival on univariable analysis (HR 1.11 for metformin treated vs untreated patients, 95% CI 0.78–1.58, p=0.55) (Table 2) or with time to castration-resistant prostate cancer (CRPC) (HR 0.87 for metformin treated vs untreated patients, 95% CI 0.64 – 1.18, p=0.37) (Supplemental Table 2).

In a multivariable analysis adjusted for treatment arm, *de novo* metastatic presentation, volume of disease, Gleason score and ECOG PS and BMI, metformin exposure were not associated with survival (HR 1.17; 95% CI: 0.82–1.67, p=0.37) (Table 2). Metformin exposure was also not associated with time to clinical progression (HR: 1.02: 95%.CI 0.75–1.39, p=0.91) in a multivariable analysis adjusted for treatment arm, volume of disease, prior local therapy, baseline PSA and Gleason score (Supplemental Table 2). In addition, PSA treatment response < 0.2 ng/mL at 12 months was 161 of 720 (22.4%) without metformin and 15 of 68 (22.1%) with metformin. As in prior publications, factors in this population that were associated with overall survival include high volume disease, and ECOG PS ≥1 (HR 1.90, 95% CI 1.47–2.44, for high vs low volume; and HR 1.50, 95% CI 1.21–1.87, for ECOG PS ≥1 vs ECOG PS 0,), and recurrent disease after prior local therapy vs de novo metastatic status (HR 0.67, 95% 0.5–0.89 for prior local therapy vs *de novo* metastatic status). After adjustment for volume of disease and *de novo* metastatic presentation, Gleason score ≥ 8 was also associated with OS (HR=1.36; p=0.03, 95% CI 1.04–1.79) but a weaker predictor of survival and is not available for all patients, given some patients have metastatic biopsies or treated based on clinical features without a tissue diagnosis.

Discussion

Features associated with metabolic health, including BMI and metformin exposure, have been reported to play a role in outcomes of patients with advanced cancers. We evaluated the effect of baseline BMI on prostate cancer outcome and baseline QOL scores, and the association between metformin exposure at baseline and survival in men with mHSPC treated with ADT+D or ADT on E3805 (CHAARTED). This post-hoc analysis assesses timely questions that patients and clinicians have related to nutritional status and whether medications like metformin may impact prostate cancer outcomes.

In the BMI analysis, we assessed both prostate cancer specific outcomes and quality of life. We found an association between BMI <25 and poorer baseline QOL by the FACT-P. We hypothesize that this is because nearly 80% of patients with BMI <25 had high volume disease, while other BMI groups had significantly lower percentage of patients with high volume disease. Men in the BMI <25 group may have had a higher BMI prior to diagnosis with prostate cancer, but cancer induced cachexia due to advanced disease may have resulted in a decline in BMI prior to enrollment and normal or underweight BMI at study entry. Cancer-associated weight loss is commonly associated with symptomatic cancer syndromes including greater fatigue and pain. As such, it is not likely that a higher BMI portends a better prognosis, but that lower BMI is associated with a greater cancer burden and the findings are due to reverse-causation. Notably, weight loss after diagnosis in breast and other cancers is an independent predictor of worse survival independent of treatment and prognostic factors, suggesting a similar relationship in other solid tumors[34].

In the exploratory metformin analysis, there was no survival benefit associated with metformin exposure in the small number of men with mHSPC treated with ADT alone or chemohormonal therapy in the CHAARTED population. There were however few men receiving metformin at baseline in the study overall, making this analysis underpowered. When considered in the context of available literature on metformin in cancer, the lack of an association between metformin and survival in the mHSPC population in CHAARTED suggests that the anticancer activity of metformin may differ by cancer type, disease state, and treatment, and that the effect may be small and difficult to differentiate in the setting of effective disease directed treatment. Similar to these findings, a *post hoc* analysis of mCRPC patients in the docetaxel arm of TAX 327, a phase 3 randomized controlled trial, failed to find an association between metformin exposure and improved OS[29]. Additionally, a recent retrospective cohort study including 2,832 men with mCRPC receiving docetaxel chemotherapy found no association between metformin exposure and prostate-cancer specific or overall survival[30]. In a prospective single arm phase 2 study in men with mCRPC, minimal single agent activity was seen with metformin alone with a ≥50% PSA decline in 5% of patients and 36% of patients were progression-free at 12 weeks[31]. These studies suggest metformin has an effect on these cancer specific outcomes, it is minimal and likely difficult to detect in advanced mCRPC patients receiving chemotherapy.

Despite our findings, this does not refute the use of metformin in patients with diabetes initiating ADT alone for advanced androgen-sensitive prostate cancer. A recently published

retrospective cohort study in a Veterans Administration population evaluated the impact of metformin on men initiating ADT, including 87,344 men treated with ADT >6 months and not receiving concurrent radiation[3]. This study found improved survival in men with diabetes mellitus on metformin (HR 0.82, 95% CI 0.78–0.86) compared to those with diabetes mellitus taking insulin who were not on metformin (HR 1.03, 95% CI 0.99–1.08). The referent group was men without diabetes. There are known antagonistic effects of metformin on cancer signaling pathways, and metformin use has been found to improve outcomes in other hormonally-mediated advanced cancers including breast and endometrial. [20, 22]. These results may be due in part to the adverse metabolic health effects of hormone ablation, which may be mitigated in diabetic men treated with metformin after ADT.[32] Metabolic syndrome has been associated with a shorter time to PSA progression and shorter OS in patients on ADT as compared with men without metabolic syndrome[33]. Nonetheless, its value as an adjunct in men receiving ADT and docetaxel is not clear, and use of metformin for men without diabetes is not supported by our data.

We acknowledge several limitations with this study as with any secondary exploratory analysis of phase 3 data. First, the absolute number of patients receiving metformin at baseline was low, possibly because patients included in clinical trials tend to have fewer comorbidities requiring treatment, including diabetes. Further, we do not have data describing specific comorbidities or concomitant diabetic or other medication use to include in the survival analysis or details describing whether patients treated with metformin had diabetes or were receiving metformin for other reasons. Having data on the indication for treatment with metformin, and information regarding comorbid cardiovascular disease, diabetes, and exposure to insulin, oral hypoglycemic or other diabetes medications, and statins could reduce confounding if this information were available. Additionally BMI and metformin exposure were calculated by a cross-sectional analysis performed only at baseline. Having data on BMI change prior to enrollment or over time during the study, and information describing metformin dose and duration of exposure over the course of the study would strengthen our analysis. In addition, we do not have data on patients taking insulin and other types of oral hypoglycemics at the time of docetaxel treatment. Finally, although metformin exposure at baseline was a pre-specified analysis, the study was not powered specifically to assess the effect of metformin exposure or BMI on OS or QOL due to the small number of exposed patients in the population, thus limiting our ability to definitively make conclusions about the effect of these factors on these outcomes despite the randomized prospective design of the study.

Conclusions

In this analysis of men with mHSPC treated on the CHAARTED study, men with low or normal BMI had evidence of more advanced cancer and a poorer baseline QOL when compared with overweight and obese men. Metformin exposure did not significantly affect prostate cancer outcomes, including survival, in men with mHSPC treated with ADT alone or ADT plus docetaxel. In the absence of a prospective randomized study designed to evaluate metformin exposure in men with mHSPC receiving ADT alone or as part of chemohormonal therapy irrespective of concurrent diabetes, there is no compelling reason to add metformin for men without diabetes. Definitive recommendations await the results of

ongoing studies investigating metformin exposure regardless of underlying use for diabetes, including in the STAMPEDE MRC trial (Clinical registration number NCT00268476) that is powered to evaluate a difference in prostate cancer specific outcomes in men with mHSPC with or without metformin exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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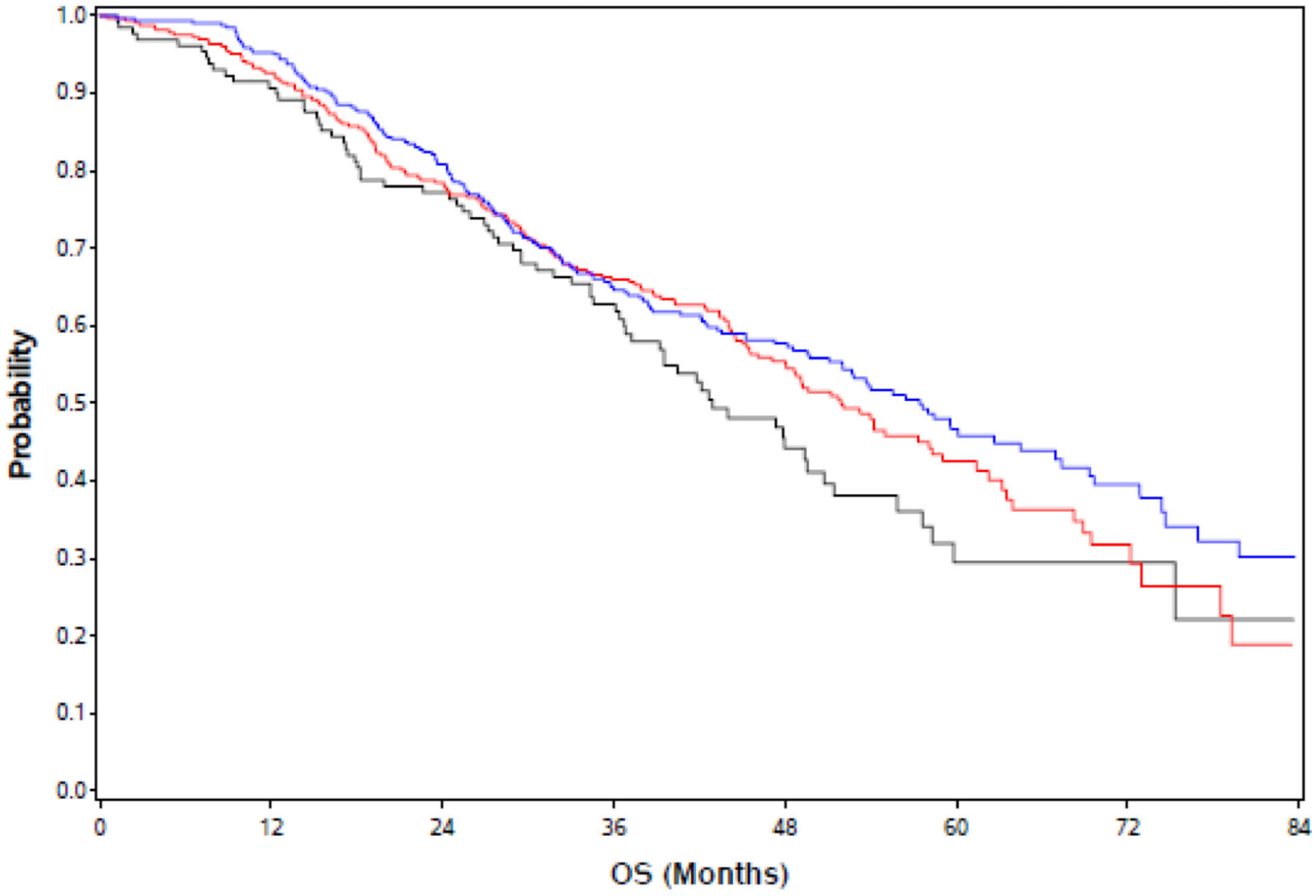
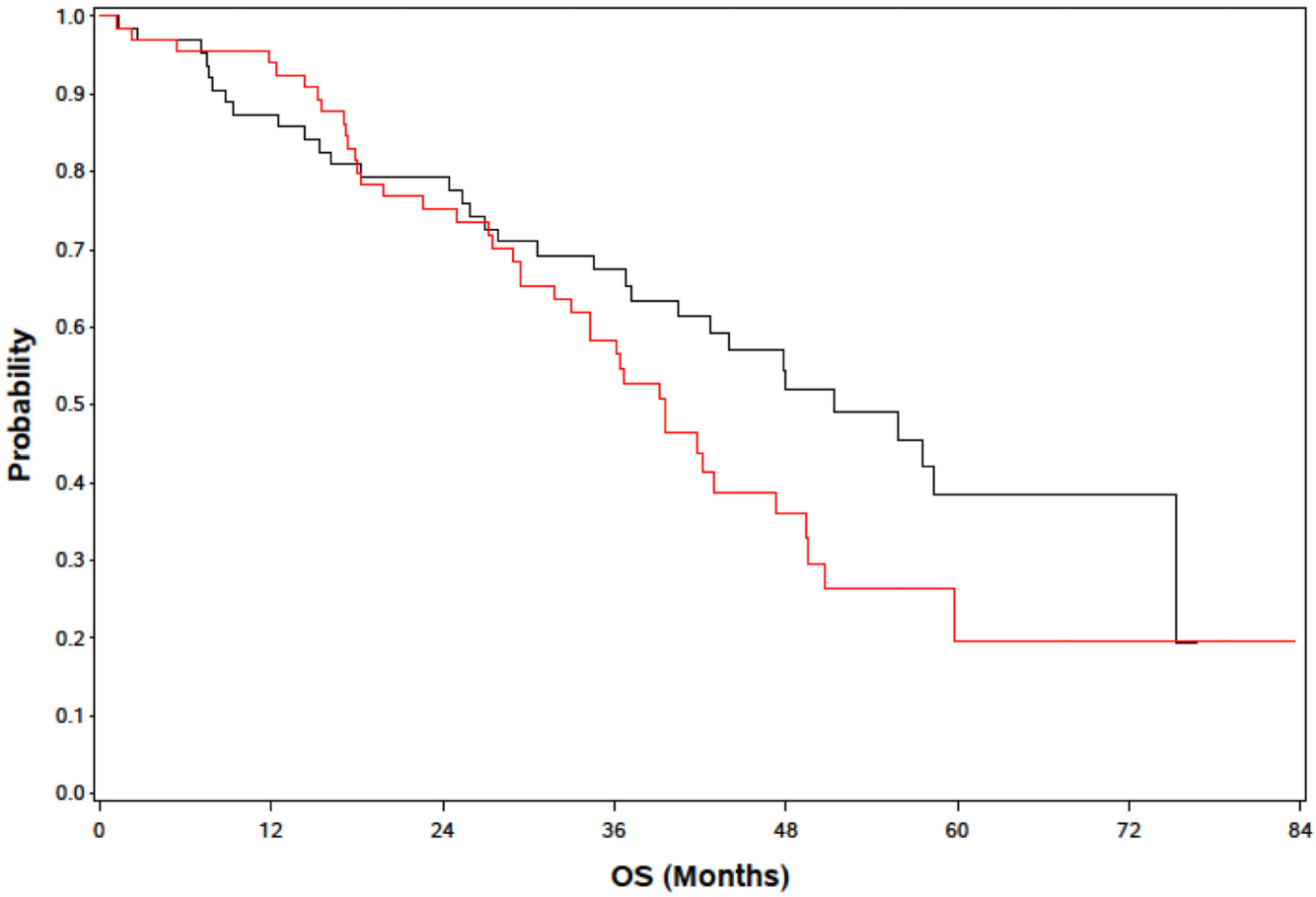
1A



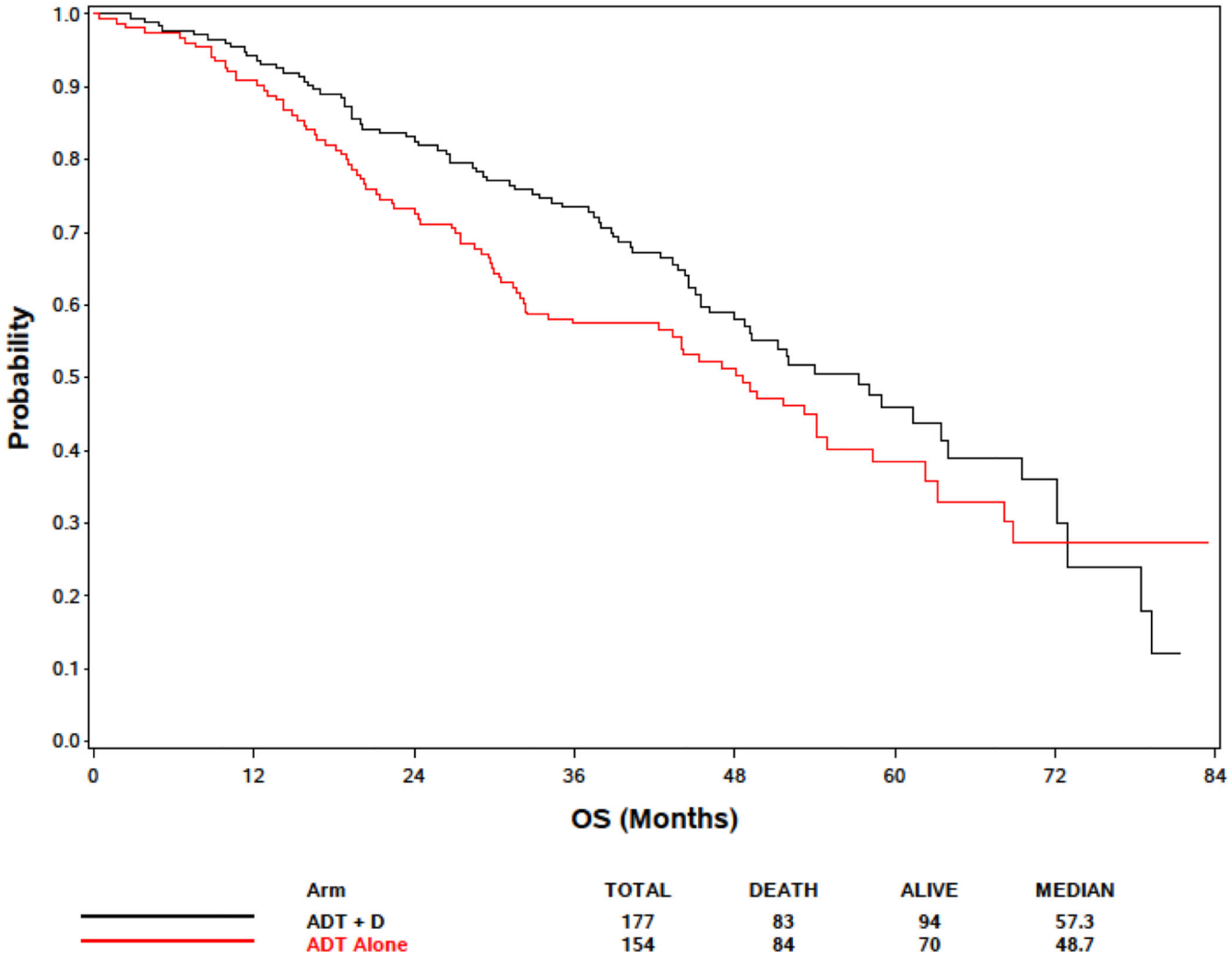
BMI	TOTAL	DEATH	ALIVE	MEDIAN
Normal/Underweight	132	72	60	42.9
Overweight	331	167	164	51.9
Obese	324	159	165	57.4

1B: BMI<25



Arm	TOTAL	DEATH	ALIVE	MEDIAN
ADT + D	64	32	32	51.4
ADT Alone	68	40	28	39.5

1C: BMI of 25-29.9



Arm	TOTAL	DEATH	ALIVE	MEDIAN
ADT + D	177	83	94	57.3
ADT Alone	154	84	70	48.7

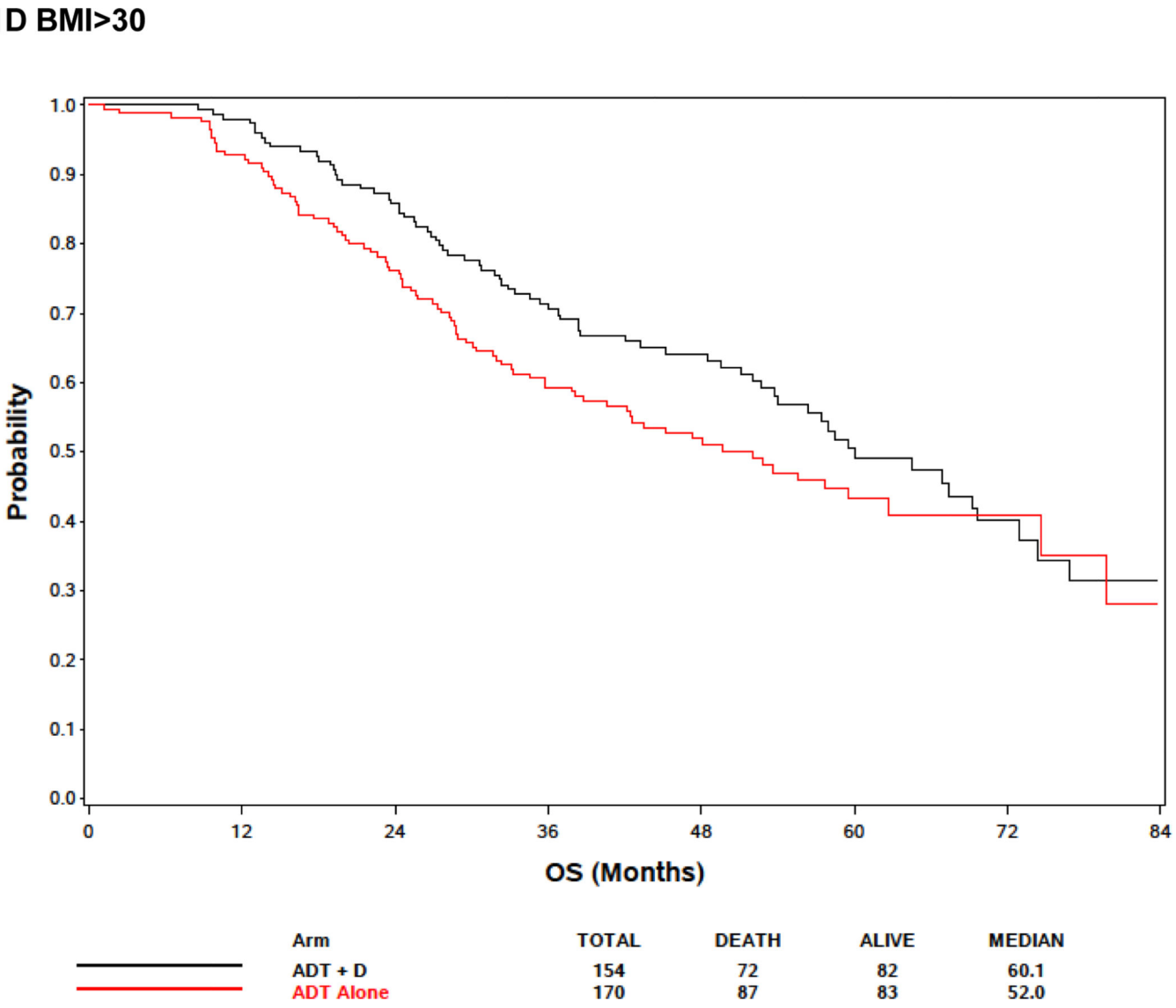


Figure 1:

Effect of body mass index (BMI) on survival. (A) Including all E3805 treatment arms, no significant survival difference was noted between patients of different BMI at study presentation, but a trend seen towards improved survival in obese patients (BMI>30) was noted (see Table 3). (B) Effect of BMI on survival comparing ADT + D versus ADT alone for BMI<25). (C) Effect of BMI on survival comparing ADT + D versus ADT alone for BMI>25<30 (D) Effect of BMI on survival comparing ADT + D versus ADT alone for BMI>30.

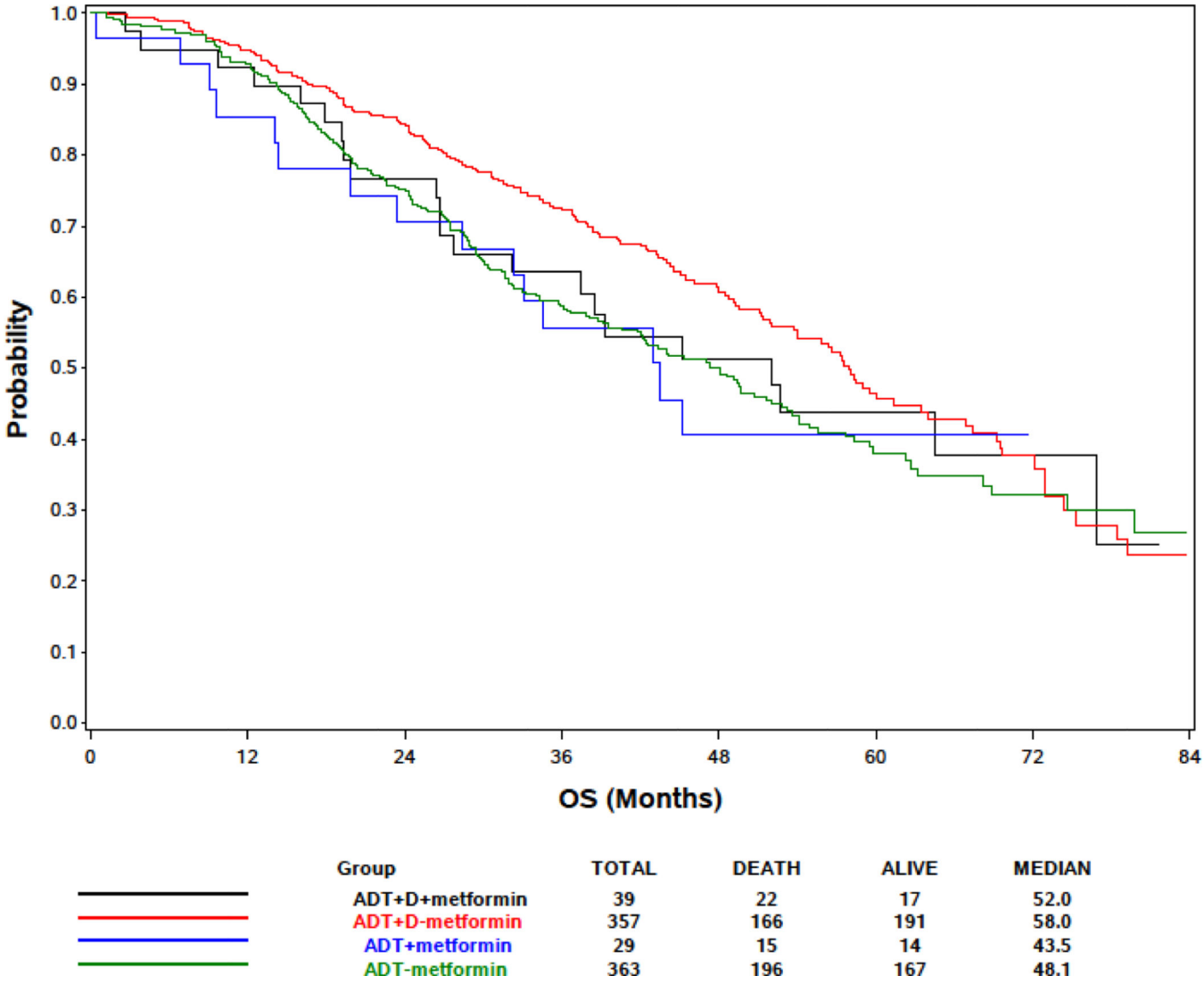


Figure 2:

Kaplan-Meier Estimates of Overall Survival Based on Metformin Use, Docetaxel (D) and Androgen Deprivation Therapy (ADT) for Patients with Metastatic Hormone Sensitive Prostate Cancer.

Table 1:

Patient Characteristics by Treatment Arm and Metformin Use

	Group									
	ADT+D+Metformin (n=39)		ADT+D (n=357)		ADT+Metformin (n=29)		ADT (n=363)		Total (n=788)	
	N	Percent	N	Percent	N	Percent	N	Percent	N	Percent
Age										
Median		66		63		63		63		63
Range		51–88		36–83		51–82		39–91		36–91
Race										
White	35	89.7	308	88.8	25	89.3	304	88.4	672	88.7
Black	4	10.3	35	10.1	3	10.7	34	9.9	76	10.0
Orient	0	.	4	1.2	0	.	6	1.7	10	1.3
Missing/Unknown	0	.	10		1		19		30	
Weight (kg)										
Median		88.3		89.8		102.4		88.6		89.7
Range		61.0–151.9		50.9–151.0		59.4–153.7		49.4–185.0		49.4–185.0
BMI										
Median		28.4		28.6		32.9		28.9		28.8
Range		21.1–47.9		16.2–48.2		20.4–45.4		17.0–56.5		16.2–56.5
BMI										
<25	4	10.3	60	16.9	2	6.9	66	18.2	132	16.8
25≤BMI<30	17	43.6	160	44.9	8	27.6	146	40.2	331	42.1
≥30	18	46.2	136	38.2	19	65.2	151	41.6	324	41.2
Missing	0		1		0		0		1	
ECOG PS										
0	27	69.2	249	69.7	17	58.6	255	70.2	548	69.5
1	12	30.8	102	28.6	12	41.4	103	28.4	229	29.1
2	0	.	6	1.7	0	.	5	1.4	11	1.4
Extent of Disease										
High	26	66.7	237	66.4	17	58.6	232	63.9	512	65.0
Low	13	33.3	120	33.6	12	41.4	131	36.1	276	35.0
Visceral Disease (among high volume)										
No	20	76.9	186	78.5	11	64.7	172	74.1	389	76.0
Yes	6	23.1	51	21.5	6	35.3	60	25.9	123	24.0
Gleason Score										
<7	3	8.3	18	5.6	1	3.8	20	6.2	42	6.0
7	9	25.0	87	27.1	7	26.9	76	23.7	179	25.4
8–10	24	66.7	216	67.3	18	69.2	225	70.1	483	68.6
Missing/Unknown	3		36		3		42		84	
Local Therapy Type										

	Group									
	ADT+D+Metformin (n=39)		ADT+D (n=357)		ADT+Metformin (n=29)		ADT (n=363)		Total (n=788)	
	N	Percent	N	Percent	N	Percent	N	Percent	N	Percent
None	29	74.4	260	72.8	22	75.9	264	72.7	575	73.0
Prostatectomy	9	23.1	71	19.9	6	20.7	67	18.5	153	19.4
Definitive RT	1	2.6	26	7.3	1	3.4	32	8.8	60	7.6
Prior Adjuvant Hormone Therapy										
No	37	94.9	341	95.5	29	100.0	347	95.6	754	95.7
Yes	2	5.1	16	4.5	.	.	16	4.4	34	4.3
Baseline PSA (ng/ml)										
Median		48.7		51.7		28.4		54.4		51.7
Range		1.1–2377		0.2–8540		0.3–2646		0.1–8056		0.1–8540
ADT Prior to Randomization										
No	7	17.9	43	12.1	3	10.3	49	13.5	102	13.0%
Yes	32	82.1%	312	87.9%	26	89.7%	314	86.5%	684	87.0%
Missing/Unknown	0		2		0		0		2	

Table 2:

Cox regression model[1] for overall survival including BMI and metformin use

	UVA (n=788[2])			MVA[3] (n=788[2])			MVA[4] (n=788[2])		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Treatment arm									
ADT alone	1.00	-		1.00	-		1.00	-	
ADT + D	0.73	(0.59, 0.89)	0.002	0.70	(0.58, 0.86)	0.0007	0.70	(0.57, 0.86)	0.0006
Metformin use									
No	1.00	-		1.00	-		1.00	-	
Yes	1.11	(0.78, 1.58)	0.55	1.15	(0.81, 1.63)	0.44	1.17	(0.82, 1.67)	0.37
Volume of disease									
Low	1.00	-		1.00	-		1.00	-	
High	2.19	(1.72, 2.79)	<.0001	1.91	(1.49, 2.45)	<.0001	1.90	(1.47, 2.44)	<.0001
ECOG PS									
0	1.00	-		1.00	-		1.00	-	
1–2	1.45	(1.17, 1.80)	0.0007	1.51	(1.22, 1.87)	0.0002	1.50	(1.21, 1.87)	0.0003
Gleason score									
≤7	1.00	-		1.00	-		1.00	-	
8–10	1.50	(1.16, 1.93)	0.002	1.36	(1.04, 1.79)	0.03	1.36	(1.04, 1.79)	0.03
Missing/Unknown	1.39	(0.94, 2.06)	0.10	1.12	(0.75, 1.67)	0.60	1.12	(0.75, 1.68)	0.58
Prior local therapy									
No	1.00	-		1.00	-		1.00	-	
Yes	0.64	(0.49, 0.84)	0.001	0.67	(0.50, 0.89)	0.005	0.67	(0.50, 0.89)	0.006
Baseline PSA									
<65	1.00	-		-	-	-	-	-	-
≥65	1.14	(0.92, 1.41)	0.23	-	-	-	-	-	-
BMI									
<25	1.00	-		-	-	-	1.00	-	
25–29.9	0.92	(0.69, 1.22)	0.55	-	-	-	0.99	(0.74, 1.32)	0.94
≥30	0.83	(0.62, 1.11)	0.21	-	-	-	0.89	(0.66, 1.19)	0.42

Variable	UVA (n=788[2])			MVA[3] (n=788[2])			MVA[4] (n=788[2])		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
BMI									
<30	1.00	-		-	-	-	-	-	-
≥30	0.88	(0.72, 1.09)	0.24	-	-	-	-	-	-

1. stratified by stratification factors at randomization, including age, ECOG PS, CAB use, duration of prior adjuvant hormonal therapy, use of FDA approved drugs for delaying skeletal related events and volume of disease; treatment arm by metformin use interaction was not statistically significant (p=0.86)

2. only patients with metformin data were included in the analysis

3. variables with p<0.10 in the univariable analysis were included in the multivariable analysis; metformin use was forced into the multivariable model regardless of significance.

4. BMI was included in the multivariable model regardless of significance per reviewers' suggestion.

Table 3:

Distribution of baseline QOL scores by BMI group

Baseline QOL	Underweight/Normal (BMI <25)		Overweight (25≤BMI<30)		Obese (BMI ≥30)		p-value[4]
	n	Median (Range)	n	Median (Range)	n	Median (Range)	
Overall							
FACT-P total[1]	116	117.8 (43.7–151.8)	293	125.0 (47.0–156.0)	294	122.9 (46.0–153.9)	**0.008**
Pain score[2]	113	1.25 (0–8.0)	270	1.0 (0–7.5)	277	1.25 (0–9.0)	**0.07**
FACIT-Fatigue[3]	116	44.0 (3.0–52.0)	289	46.0 (6.0–52.0)	299	43.3 (0–52.0)	**0.004**
ADT+D							
FACT-P total[1]	56	116.3 (75.0–151.8)	162	124.0 (47.0–156.0)	140	122.9 (51.0–153.9)	0.18
Pain score[2]	55	1.25 (0–8.0)	147	0.75 (0–7.0)	133	1.0 (0–9.0)	0.46
FACIT-Fatigue[3]	56	44.5 (14.0–52.0)	158	46.0 (9.0–52.0)	145	44.0 (5.0–52.0)	0.23
ADT alone							
FACT-P total[1]	60	120.0 (43.7–151.0)	131	127.5 (54.0–153.9)	154	122.8 (46.0–152.0)	**0.03**
Pain score[2]	58	1.13 (0–7.25)	123	1.0 (0–7.5)	144	1.25 (0–8.0)	0.14
FACIT-Fatigue[3]	60	43.0 (3.0–52.0)	131	46.0 (6.0–52.0)	154	43.0 (0–52.0)	**0.01**

1. Higher scores indicate better QOL. Clinically meaningful change on the FACT-P total score is considered a change of 6–10 points.

2. Higher scores indicate greater pain.

3. Higher scores indicate improved fatigue.

4. Comparison among 3 BMI groups using Kruskal-Wallis test

Table 4:

Distribution of overall survival by treatment arm and metformin use

	ADT+D+metformin (n=39)	ADT+D/No metformin (n=357)	ADT+metformin (n=29)	ADT/No metformin (n=363)
Overall survival (months)				
Median	52.0	58.0	43.5	48.1
95% CI	27.7, 76.9	52.1, 63.9	23.5, NA	40.7, 53.3
Number of deaths	22	166	15	196
Number of PC deaths	15	132	12	164
p-value (stratified * logrank)	0.31 (compare metformin y/n in ADT+D arm)		0.76 (compare metformin y/n in ADT alone arm)	

* stratified on stratification factors at randomization