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Outcomes of Older Men Receiving Docetaxel for Metastatic Hormone-Sensitive Prostate Cancer

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Abstract

Background: Most men who die of prostate cancer are older than 70 years. The ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) randomized men of all ages with metastatic hormone-sensitive prostate cancer (mHSPC) to receive androgen deprivation therapy (ADT) with or without docetaxel demonstrating an overall survival (OS) benefit for docetaxel.

Methods: In a post-hoc analysis of this trial, we assessed patient characteristics and OS in patients ≥70 years ("older men") versus <70 years ("younger men") with Cox proportional hazards models. Additionally, we compared adverse events, therapy completion rate, and subsequent treatment patterns between these two groups using Chi-squared tests.

Results: 177 (22.4%) patients were ≥70 years. Docetaxel + ADT resulted in improved OS in both older and younger men (Hazard Ratio [HR] 0.45, 95%CI: 0.25–0.80 for older men; HR 0.71, 95%CI: 0.53–0.95 for younger men). This treatment benefit was seen for subgroups of older men with high volume disease (HR 0.43, 95%CI 0.23–0.79) and de novo metastatic disease (HR 0.36, 95%CI 0.19–0.69). A similar proportion of older and younger men completed six cycles of docetaxel (82.6% vs. 87.1%, p=0.28). Rates of grade 3–5 adverse events were similar between older and younger men (36.8% vs. 26.8%, respectively, p=0.069). The rate of any Grade 4–5 adverse events did not differ significantly between older and younger men (14.9% vs. 11.9%, respectively, p=0.46). In the control arm, a smaller proportion of older men received subsequent cancer treatments (34.4% vs. 51.5%, p=0.017) or subsequent docetaxel (25.6% vs. 37.6%, p=0.035) compared to younger men.

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Availability of Data: We obtained the data from CHAARTED through the National Clinical Trials Network (NCT00309985-D3 and NCT00309985-D4). Data were originally collected from clinical trial NCT00309985. The data are publicly available through the NCTN.

Conclusions: Older men with mHSPC had similar OS benefit and clinical outcomes compared to younger men when receiving docetaxel + ADT. Oncologists should consider docetaxel chemotherapy as a favorable treatment option for older men with mHSPC who are fit for chemotherapy.

Introduction:

Prostate cancer is the second-leading cause of cancer death among males,[1] and two-thirds of men who ultimately die of prostate cancer are over the age of 75.[2] According to Surveillance, Epidemiology, and End Results (SEER) registry data, men with de novo metastatic prostate cancer aged 75 or older have inferior prostate cancer specific mortality (PCSM) compared to men 54 years old or younger.[3] Specifically, their overall survival is on average 6.7 months shorter with an adjusted 49% increase in the rate of PCSM.[3] Several pivotal clinical trials in the past several years have shown that both chemotherapy and novel hormonal agents, including docetaxel,[4,5] abiraterone,[6,7] apalutamide,[8] and enzalutamide[9,10] prolong the longevity of men with metastatic hormone sensitive prostate cancer (mHSPC), establishing new standards of care for this population.

Oncologists face a particular challenge in clinical practice when deciding between these options for men with mHSPC.[11] This decision is more difficult in older adults, in whom comorbidities or concerns about tolerance of treatment may affect decision-making.[12–15] Indeed, the high prevalence of both undertreatment and overtreatment in older adults with advanced cancer is well-established in the geriatric oncology literature.[13] For this patient population, geriatric assessment has been shown to decrease toxicity but is not routinely performed due to the time and resources required.[13,15–17] In older men with mHSPC, oncologists may be hesitant to use cytotoxic chemotherapy with docetaxel and instead favor hormonal approaches such as abiraterone, enzalutamide, or apalutamide.

In CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer), docetaxel was given at a dose of 75mg/m^2 with dexamethasone every three weeks for a total of six cycles, along with standard androgen deprivation therapy (ADT). CHAARTED showed that the overall survival benefit with docetaxel was mainly seen in men with high-volume disease, defined as a visceral metastasis or four or more bony metastases, of which at least one is outside of the spine or pelvis.[18] A subgroup analysis showed that older men in the trial, defined as age greater than or equal to 70, had a similar survival benefit compared to younger men.[5]

To better understand the outcomes of older men receiving docetaxel for mHSPC, we conducted a post-hoc analysis of CHAARTED. Specifically, we first compared the clinical characteristics of older versus younger men in CHAARTED. We then analyzed the results of the trial in order to better understand differences in clinical outcomes, therapy completion rate, tolerance of treatment, and adverse events between older and younger men.

Methods

Study Design and Participants

We obtained the data from CHAARTED through the National Clinical Trials Network (NCT00309985-D3 and NCT00309985-D4). Data were originally collected from clinical trial NCT00309985. All analyses and conclusions are the sole responsibility of the authors and do not necessarily reflect the opinions or views of the clinical trial investigators, the NCTN, the NCORP, or the NCI. The results of the trial have previously been reported.[5,18]

In brief, this multicenter, randomized, open-label phase III trial, funded by the National Cancer Institute, included 790 patients with metastatic hormone-sensitive prostate cancer with adequate organ function and Eastern Cooperative Oncology Group (ECOG) performance status of zero to two. Eligible patients enrolled in the trial from July 2006 to December 2012. All patients who participated in CHAARTED were included in this analysis, with a follow-up data cutoff date of 12/23/2014.

The trial dataset identified men as either 70 years or older (“older men”) or younger than 70 years (“younger men”), and we conducted analyses comparing these two groups. The trial dataset contained information on clinical and demographic characteristics, Gleason score, disease volume (high versus low volume), prior local therapy for prostate cancer, overall survival and prostate-cancer specific outcomes. The dataset also included information on subsequent cancer treatment patterns, tolerance of treatment, and adverse events.

Statistical Analyses

We analyzed categorical variables with Chi-squared tests and skewed continuous variables using Wilcoxon rank-sum tests. Overall survival, by age, was calculated using the Kaplan-Meier method, and hazard ratios for subgroup analyses were calculated using Cox proportional hazards models. Using these same Cox proportional hazards models, we calculated the interaction term between the treatment arm and age, overall and by subgroups (high volume disease, low volume disease, de novo metastatic disease). We used Chi-squared tests to assess differences by age in PSA level <0.2 at 6 and 12 months. Per the original study’s approach, we first described overall adverse events first in the entire sample, by age, and then used Chi-squared tests to assess differences in rates of Grade 3–5 and Grade 4–5 toxicities at the patient-level.

Results

Patient Characteristics

Out of 790 men in CHAARTED, there were 177 (22.4%) men age 70 or greater and 613 (77.6%) men less than 70 years old (Table 1). Older men were more likely to be White and less likely to be Black. Older men were more likely to have an impaired performance status, with 36.7% having an ECOG performance status of one or two, compared to 28.6% of younger men (p=0.038).

Similar proportions of older men versus younger men had high volume disease (65.0% vs. 64.9%, p=0.99) and visceral metastases (14.7% vs. 15.8%, p=0.69). Older men were

significantly more likely to have a lower Gleason score (p=0.003 for overall comparison), with 10.7% of older men having a Gleason score of four to six compared to 3.8% of younger men. Older men had lower PSA levels at the start of ADT, with a median PSA of 32.8 (IQR 10.3–182.7) vs. 58.2 (IQR 14.8–310.0) in younger men (Wilcoxon rank-sum test p=0.01). Older men were more likely to have had prior local treatment, with 16.4% having had prior radiation therapy, compared to 5.1% of younger men (p<0.001 for overall comparison).

Clinical Outcomes

Overall survival by age is shown graphically in Figure 1. As reported in CHAARTED, the hazard ratios for death in those who received docetaxel + ADT versus ADT alone showed benefit of docetaxel in both age groups (HR 0.45, 95% CI 0.25–0.80, for older men; HR 0.71, 95% CI 0.53–0.95 for younger men; HR for interaction=0.60, p=0.125).[5] In subgroup analysis by volume status and prior local treatment, several important findings emerged (Figure 2). The benefit of docetaxel in high-volume disease was seen both for younger and older men, and there was no benefit of docetaxel in low-volume disease in either younger or older men. Notably, the benefit of docetaxel for men with de novo metastatic disease was demonstrated in older men (HR 0.36, 95% CI 0.19–0.69), but did not reach significance among younger men (HR 0.75, 95% CI 0.55–1.03). All interaction terms for these subgroup analyses were not significant, except for the interaction term between treatment arm and age among patients with de novo metastatic disease (HR for interaction 0.462, p=0.03).

In terms of other clinical outcomes, the benefit of docetaxel regarding time to castration-resistant prostate cancer (CRPC) and time to clinical progression was shown in both older and younger men (Table 2). Specifically, median time to CRPC among older men was 29.2 months for the ADT + Docetaxel group versus 14.7 months in the ADT alone group (HR 0.60, 95% CI 0.41–0.87, p=0.008), whereas in younger men, median time to CRPC was 18.1 months in the ADT + Docetaxel group versus 11.4 months in the ADT alone group (HR 0.65, 95% CI 0.54–0.79, p<0.001). Results were similar for time to clinical progression. The benefit of docetaxel on rates of PSA complete response at 6 months and 12 months in older men was similar to that of younger men.

Treatment Course and Adverse Events

Tolerability of treatment was similar regardless of age. Older men receiving docetaxel had a similar proportion of dose modifications compared to younger men (26.7% vs. 26.4%, p=0.95), and a similar proportion in both age groups received all six cycles of docetaxel (82.6% vs. 87.1%, p=0.28) (Table 3A). 36.8% of older men in the treatment arm experienced any Grade 3–5 adverse event compared to 26.8% of younger men (p=0.069). The rates of any Grade 4–5 adverse events did not differ significantly between age groups (14.9% of older men vs. 11.9% of younger men, p=0.46). Older men experienced more hematologic toxicity, with all Grade 3–4 anemia and thrombocytopenia occurring among this group (n=6 events). However, neutropenia (including febrile neutropenia and infection with neutropenia) represented a similar proportion of all adverse events in older and younger men. The only two cases of Grade 3 motor neuropathy were among older men. One patient each in the younger and older category developed Grade 3 sensory neuropathy. The single Grade 5 event of sudden death occurred in a younger man with pre-existing lung disease.

In terms of subsequent cancer therapy, older men in the control arm were less likely to receive subsequent cancer-directed treatments (Table 3B). Specifically, 65.6% of older men in the control arm received no subsequent cancer-directed treatments compared to 48.5% of younger men (p=0.017). This difference was not seen in the ADT + docetaxel group, where similar proportions of men received no subsequent life prolonging treatments (70.1% of older men vs. 60.0% of younger men, p=0.22). When analyzing specific subsequent treatments administered to older versus younger men, older patients in the control arm were significantly less likely to receive docetaxel (25.6% vs. 37.6%, p=0.035) and other approved treatments for CRPC compared to younger men. Older men in the treatment arm were also less likely to receive docetaxel in subsequent lines of therapy (5.7% vs. 15.8%, p=0.016), though they had similar rates of receipt of other types of subsequent therapies for CRPC as younger men. Among patients who died within the study period, the causes of death were similar between older and younger men, with 14 (78%) older men dying due to prostate cancer versus 71 (86%) younger men (p=0.76).

Discussion

Our findings demonstrate that older men with metastatic hormone-sensitive prostate cancer who were eligible to participate in a randomized trial and receive ADT + docetaxel versus ADT alone had similar clinical outcomes compared to younger men. In terms of overall survival, older men with high-volume disease and de novo metastatic disease receiving docetaxel had at least as great, and possibly even greater, benefit from docetaxel compared to younger men. Further, older men tolerated treatment well and had a similar adverse events profile compared to younger men, with over 80% of patients completing all six cycles of treatment and about one-third experiencing Grade 3–5 adverse events. Only one quarter of older men in the control group went on to receive docetaxel, reflecting a possible bias against administering cytotoxic chemotherapy in older men. Given the known inferior survival of older men with metastatic prostate cancer,[3] these findings highlight two important points: one, that docetaxel should be routinely used to improve clinical outcomes in fit older men with high-volume metastatic hormone-sensitive prostate cancer, and two, that providers must overcome a preexisting reluctance to treat older men with docetaxel when they are fit for chemotherapy.

Given that the treatment goal in metastatic prostate cancer is to prolong life and manage cancer-related symptoms, oncologists' primary approach to this population is to sequence cancer treatments in a manner that can improve survival while maintaining quality of life. A major benefit of docetaxel in first-line treatment for mHSPC for older men with high-volume disease is that the treatment and most of its side effects are limited to six cycles of therapy, after which patients are on ADT alone, often for years. For other hormonal treatments in this setting, treatment and its side effects are usually indefinite. Further, the costs and subsequent financial toxicity are significantly less with chemotherapy than with hormonal agents.[19,20] The delay in time to mCRPC found among older men, which was seven months longer than for younger men, could also have benefits from delaying toxicities from treatment in the CRPC setting. This delay in time to mCRPC in older men may also be due to less aggressive disease at baseline, as indicated by lower Gleason scores and baseline

PSA values compared to younger men. Moreover, the "older" men accrued may have been generally fitter.

While the reported receipt of docetaxel for mCRPC in the control group at time of data analysis was low overall it is probably an under-estimate as many men may have responded to other agents such as abiraterone and responded for many months prior to getting docetaxel. Our finding that only one quarter of older men in the control arm ultimately received docetaxel, a significantly lower proportion than among younger men, may reflect oncologists' reluctance to offer older adults cytotoxic chemotherapy in the mCRPC setting or older adults' preferences against it, but also could indicate that these men may have developed age-related health decline and may not have been fit enough for chemotherapy after initial mHSPC treatment. Thus, in addition to the established superior survival benefit for docetaxel in the hormone-sensitive versus castration-resistant setting,[5,18,21] these findings may indicate that the hormone-sensitive state could be the best chance to offer the survival benefits of docetaxel and hormonal therapy to older men, before changes in performance status or chemotherapy fitness may preclude docetaxel use in the CRPC setting.

The finding that performance status was worse among older men in this trial, yet outcomes were similar to younger men with no appreciable increase in non-prostate cancer related death raises the possibility that impaired performance status in this trial was more reflective of cancer-related impairment in functional status rather than general frailty or global measures of function. Performance status measurement itself is controversial,[22] and many argue that geriatric assessment captures fitness for chemotherapy better than traditional performance status measures alone.[12,14–16,23] Further studies are needed to examine outcomes of older men with metastatic prostate cancer who have impaired performance status due to frailty or comorbidities, along with studies of geriatric assessment and treatment decision-making in this population.

Limitations

The study of older adults in the clinical trial setting limits the generalizability of these results. Most importantly, there is selection bias in terms of which older adults were referred to and enrolled in a clinical trial that included chemotherapy. CHAARTED did have a younger median age than other prior studies of hormonal therapies.[6–10] However, for fit older adults who would be clinical trial candidates, these findings are likely still applicable.

We did not have access to detailed geriatric assessments or functional assessments that would have helped us differentiate which geriatric conditions are associated with better or worse outcomes, and we also did not have access to detailed age data that would allow us to provide further details on outcomes for the oldest men, which may differ from those closer to age 70. Analysis of further lines of therapy is limited by the fact that many novel CRPC therapies were not approved until later in the trial period, after 2011, meaning some patients may not have had access to these drugs at progression. Future studies should seek to enroll a greater proportion of older adults, per recent American Society of Clinical Oncology and Food & Drug Administration recommendations,[24] as well as make use of real-world data to study outcomes of older men receiving docetaxel plus ADT as first-line treatment for

mHSPC. These studies would ideally help determine the optimal sequencing of treatments for older men with metastatic prostate cancer.

Conclusion

In summary, our study demonstrates that older men treated with docetaxel along with ADT for high-volume and de novo mHSPC had similar benefit in overall survival and other clinical outcomes when compared to younger men. Adverse event profiles were similar between groups, and older men were less likely to receive docetaxel in the castration-resistant setting. Oncologists should consider docetaxel chemotherapy as a favorable initial treatment option for older men with high-volume metastatic hormone-sensitive prostate cancer who are fit for chemotherapy.

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Conflicts of Interest: Richard J. Lee reports consulting role for Bayer, Janssen, Astellas, and Dendreon. Joseph A. Greer reports research funding from Gaido Health/BCG Digital Ventures, NCCN/AstraZeneca (Inst); royalties from Springer (Humana Press); consulting role for Concerto HealthAI. Jennifer S. Temel reports research funding from Astra Zeneca and Pfizer. Christopher J. Sweeney reports consulting role for Sanofi, Janssen, Astellas Pharma, Bayer, Genentech, AstraZeneca, Pfizer, Lilly; research funding from Janssen Biotech (Inst), Astellas Pharma (Inst), Sanofi (Inst), Bayer (Inst), Sotio (Inst), Dendreon (Inst); patents/royalties from Pathenolide (Indiana University), dimethylaminoparthenolide (Leuchemix), Exelixis: Abiraterone plus cabozantinib combination; stock ownership in Leuchemix. No other conflicts of interest were identified.

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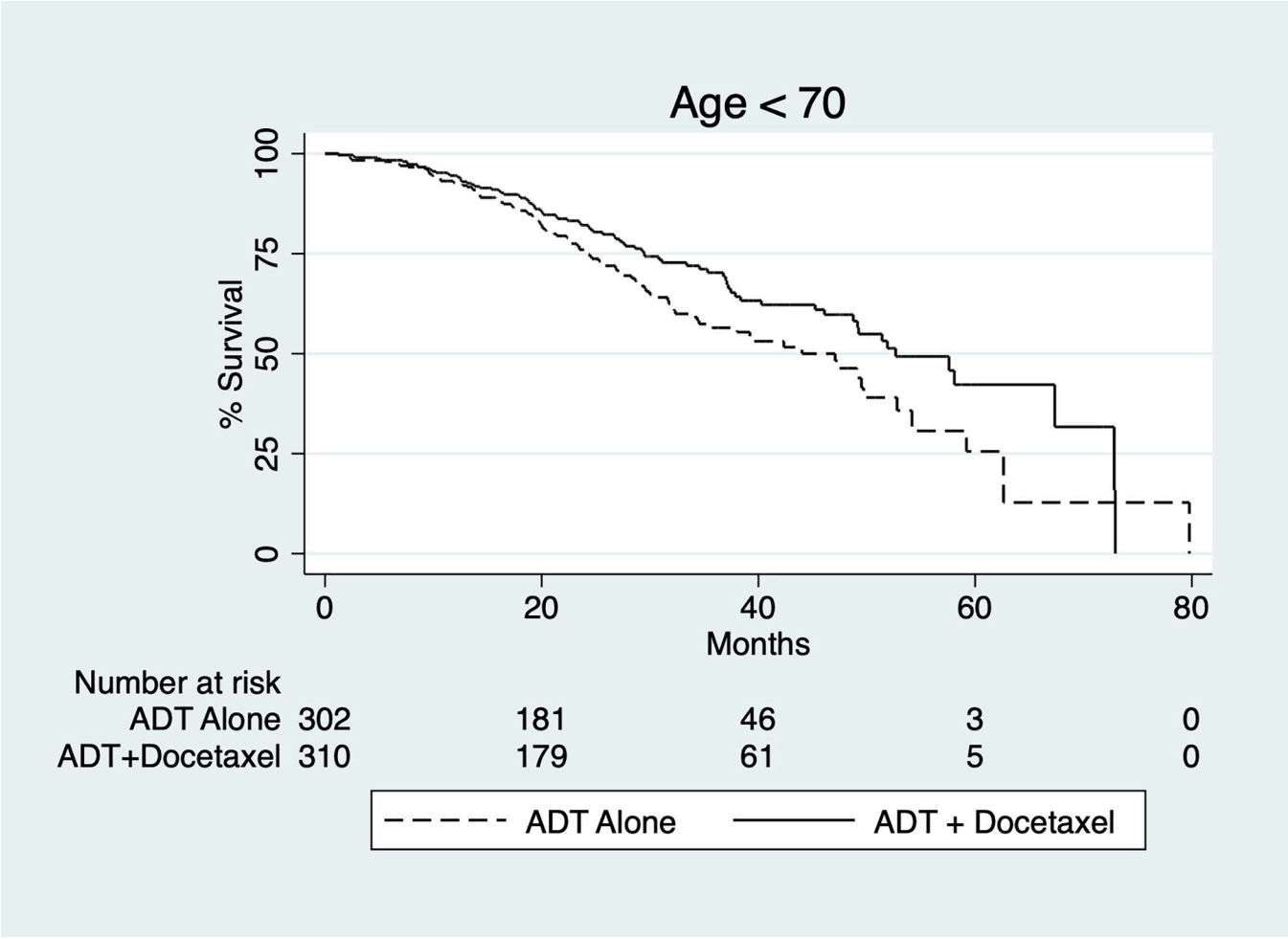

Figure 1:
Overall Survival, by Age (Age < 70)

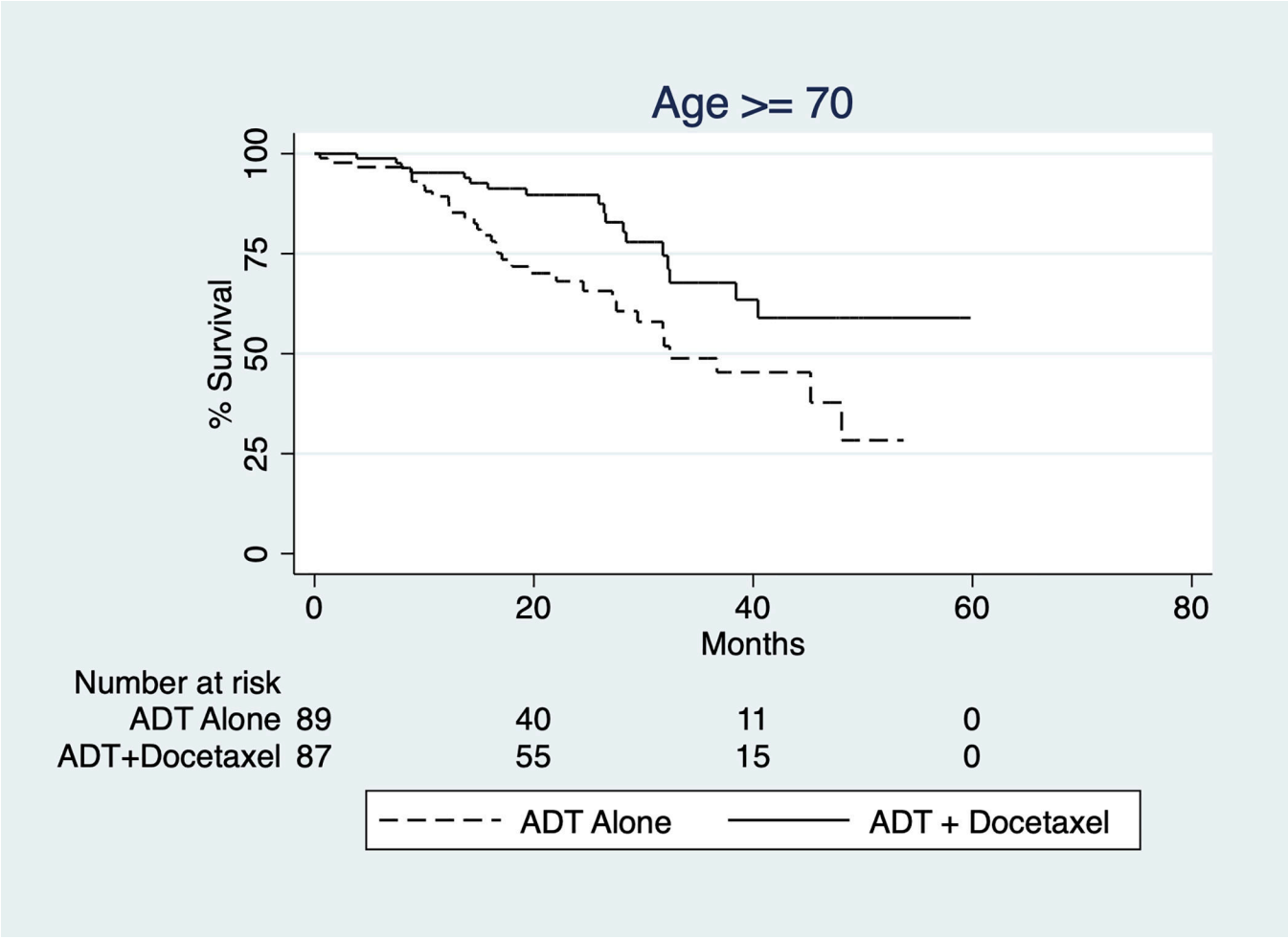

Figure 2:
Overall Survival, by Age (Age >= 70)

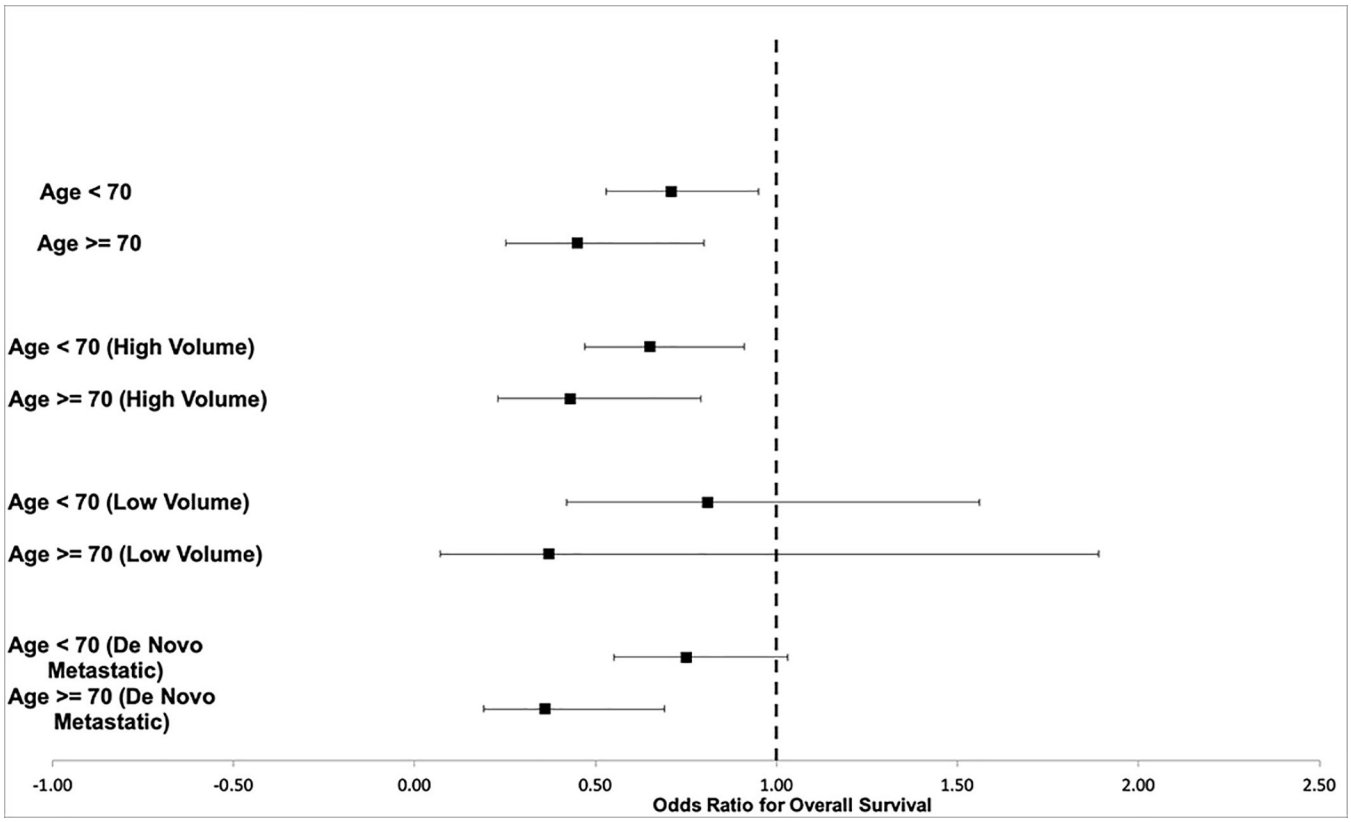

Figure 3:
Overall Survival, by Age and Other Clinical Features

Table 1:

Patient Characteristics, by Age

	Age < 70	**Age >= 70**	
	n=613	**n=177**	**p-value**
Race - no. (%)			
White	518 (84.5%)	156 (88.1%)	**0.037**
Black	63 (10.3%)	13 (7.3%)	
Other	5 (0.8%)	5 (2.8%)	
Unknown	27 (4.4%)	3 (1.7%)	
Performance Status - no. (%)			
0	437 (71.4%)	112 (63.3%)	**0.038**
1–2	175 (28.6%)	65 (36.7%)	
Volume of Metastases - no. (%)			
High	398 (64.9%)	115 (65.0%)	0.99
Low	215 (35.1%)	62 (35.0%)	
Visceral Metastases - no. (%)	97 (15.8%)	26 (14.7%)	0.69
Gleason Score			
4–6	23 (3.8%)	19 (10.7%)	**0.003**
7	137 (22.3%)	42 (23.7%)	
8–10	384 (62.6%)	100 (56.5%)	
Unknown	69 (11.3%)	16 (9.0%)	
PSA level at start of ADT -- ng/mL			
Median (IQR)	58.2 (14.8, 310.0)	32.8 (10.3, 182.7)	**0.01**
Prior Local Treatment - no. (%)			
None	454 (74.2%)	121 (68.4%)	**<0.001**
Prostatectomy	127 (20.8%)	27 (15.3%)	
Definitive Radiation Therapy	31 (5.1%)	29 (16.4%)	
Prior Adjuvant ADT - no. (%)	19 (3.1%)	15 (8.5%)	**0.002**
Time from start of ADT to randomization - mo.			
Median (IQR)	−1.0 (−2.0, −0.4)	−1.0 (−2.0, −0.5)	0.8
No ADT before randomization - no. (%)	77 (12.6%)	26 (14.8%)	0.45

ADT (Androgen Deprivation Therapy); IQR (Interquartile Ratio)

Table 2:

Clinical Endpoints, by Age

	Age < 70	Age < 70	p-value	Age >= 70	Age >= 70	p-value
	ADT	ADT + Docetaxel		ADT	ADT + Docetaxel	
	n=303	n=310		n=90	n=87	
PSA Level < 0.2 at 6 months - no. (%)	54 (17.8%)	97 (31.3%)	<0.001	23 (26%)	30 (34%)	0.19
PSA Level < 0.2 at 12 months - no. (%)	48 (15.8%)	86 (27.7%)	<0.001	18 (20%)	24 (28%)	0.24
Time to CRPC - mo.						
Median	11.4	18.1	<0.001	14.7	29.2	0.008
95% CI	10.3–14.0	15.7–22.5		7.3–19.6	18.7–43.3	
Time to Clinical Progression - mo.						
Median	11.3	17.8	<0.001	14.7	29.2	0.008
95% CI	9.9–13.7	15.6–22.1		6.8–18.9	18.7–40.9	

ADT (Androgen Deprivation Therapy); PSA (Prostate-Specific Antigen); CRPC (Castration-Resistant Prostate Cancer)

Table 3A:

Treatment Course and Adverse Events within Treatment Arm, by Age

	Age <70			Age >= 70			*p-value*
Any Dose Modifications - no. (%)	80 (26.4%)			23 (26.7%)			0.95
Received all 6 Cycles of Docetaxel- no. (%)	264 (87.1%)			71 (82.6%)			0.28
Any Adverse Events (Grade 3–5 Combined) - no. (%)	83 (26.8%)			32 (36.8%)			0.069
Any Adverse Events (Grade 4–5 Combined) - no. (%)	37 (11.9%)			13 (14.9%)			0.46
	Grade 3	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**	
Allergic Reaction	7 (8%)	1 (2%)					
Fatigue	9 (10%)			7 (16%)			
Diarrhea	3 (3%)			1 (2%)			
Stomatitis	1 (1%)			1 (2%)			
Neuropathy, motor				2 (5%)			
Neuropathy, sensory	1 (1%)			1 (2%)			
Thromboembolism	1 (1%)	1 (2%)			1 (5%)		
Sudden Death			1 (100%)				
Anemia				4 (9%)	1 (5%)		
Thrombocytopenia					1 (5%)		
Neutropenia	9 (10%)	24 (60%)		3 (7%)	11 (50%)		
Febrile Neutropenia	10 (11%)	6 (15%)		5 (11%)	3 (14%)		
Infection with Neutropenia	3 (3%)	3 (8%)		2 (5%)	1 (5%)		
Other Adverse Event	47 (52%)	5 (12%)		18 (41%)	4 (18%)		
Total Adverse Events	91	40	1	44	22		

* Denominator for percentages is total adverse events of each particular grade. Patients may have had more than one adverse event.

Table 3B:

Treatment Course, by Age

	Control Arm			Treatment Arm		
	Age < 70	**Age >= 70**	***p-value***	**Age < 70**	**Age >= 70**	***p-value***
	303	**90**		**310**	**87**	
Number of Subsequent Cancer-Directed Treatments						
0	147 (48.5%)	59 (65.6%)	0.017	186 (60.0%)	61 (70.1%)	0.22
1	86 (28.4%)	18 (20.0%)		66 (21.3%)	13 (14.9%)	
2	70 (23.1%)	13 (14.4%)		58 (18.7%)	13 (14.9%)	
Subsequent Treatments						
Docetaxel	114 (37.6%)	23 (25.6%)	0.035	49 (15.8%)	5 (5.7%)	0.016
Cabazitaxel	36 (11.9%)	1 (1.1%)	0.002	49 (15.8%)	8 (9.2%)	0.12
Mitoxantrone or Platinum	26 (8.6%)	1 (1.1%)	0.014	26 (8.4%)	3 (3.4%)	0.12
Abiraterone or Enzalutamide	88 (29.0%)	16 (17.8%)	0.033	85 (27.4%)	20 (23.0%)	0.41
Antiandrogen or Ketoconazole	72 (23.8%)	19 (21.1%)	0.6	64 (20.6%)	16 (18.4%)	0.64
Sipuleucel T	16 (5.3%)	3 (3.3%)	0.45	16 (5.2%)	6 (6.9%)	0.53
Radiation Therapy	67 (22.1%)	12 (13.3%)	0.068	58 (18.7%)	11 (12.6%)	0.19
Cause of Death Among Decedents - no. (%)						
Due to Protocol Treatment	N/A	N/A	0.12	1 (1%)	0 (0%)	0.76
Due to Prostate Cancer	90 (87.4%)	24 (72.7%)		71 (86%)	14 (78%)	
Other Cause	6 (5.8%)	5 (15.2%)		6 (7%)	2 (11%)	
Unknown/Missing	7 (6.8%)	4 (12.1%)		5 (6%)	2 (11%)	