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Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer

Alicia K. Morgans
Northwestern University


Yu-Hui Chen
Dana Farber Cancer Institute

Christopher J. Sweeney
Dana Farber Cancer Institute

David F. Jarrard
University of Wisconsin - Madison

Elizabeth R. Plimack
Fox Chase Cancer Center

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Authors

Alicia K. Morgans, Yu-Hui Chen, Christopher J. Sweeney, David F. Jarrard, Elizabeth R. Plimack, Benjamin A. Gartrell, Michael A. Carducci, Maha Hussain, Jorge A. Garcia, David Cella, Robert S. DiPaola, and Linda J. Patrick-Miller

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Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer

Alicia K. Morgans, Yu-Hui Chen, Christopher J. Sweeney, David F. Jarrard, Elizabeth R. Plimack, Benjamin A. Gartrell, Michael A. Carducci, Maha Hussain, Jorge A. Garcia, David Cella, Robert S. DiPaola, and Linda J. Patrick-Miller

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Alicia K. Morgans, MD, MPH, Department of Medicine, Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, NMH/Arkes Family Pavilion, 676 N St Clair St, Suite 850, Chicago, IL 60611; e-mail: alicia.morgans@northwestern.edu.

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A B S T R A C T

Purpose

Chemohormonal therapy with docetaxel and androgen deprivation therapy (ADT+D) for metastatic hormone-sensitive prostate cancer improves overall survival as compared with androgen deprivation therapy (ADT) alone. We compared the quality of life (QOL) between patients with metastatic hormone-sensitive prostate cancer who were treated with ADT+D and those who were treated with ADT alone.

Methods

Men were randomly assigned to ADT+ D (six cycles) or to ADT alone. QOL was assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P), FACT-Taxane, Functional Assessment of Chronic Illness Therapy-Fatigue, and the Brief Pain Inventory at baseline and at 3, 6, 9, and 12 months. The Wilcoxon signed rank test was used to examine changes over time. Mixed-effect models compared the QOL between arms at each time point.

Results

Seven hundred ninety men were randomly assigned (ADT+D [n = 397] and ADT [n = 393]) and completed FACT-P (90% at baseline, 86% at 3 months, 83% at 6 months, 78% at 9 months, and 77% at 12 months). ADT+D patients reported a statistically significant decline in FACT-P at 3 months ($P < .001$) but FACT-P did not differ significantly between baseline and 12 months ($P = .38$). ADT+D FACT-P scores were significantly lower at 3 months ($P = .02$) but significantly higher at 12 months ($P = .04$) when compared with ADT FACT-P scores. Differences did not exceed the minimal clinically important difference at any time point. ADT+D patients reported significantly lower Functional Assessment of Chronic Illness Therapy-Fatigue scores at 3 months than did ADT patients ($P < .001$). Over time, both arms reported significantly poorer FACT-Taxane scores ($P < .001$) when compared with baseline. Brief Pain Inventory scores were similar between arms.

Conclusion

Although ADT+D was associated with statistically worse QOL at 3 months, QOL was better at 12 months for ADT+D patients than for ADT patients. Both arms reported a similar minimally changed QOL over time, suggesting that ADT+D is not associated with a greater long-term negative impact on QOL.

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ASSOCIATED CONTENT



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Appendix
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Data Supplement
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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer diagnosed in men worldwide, and is the third leading cause of cancer death among American men.^{1,2} Two landmark studies have demonstrated prolonged survival for men with metastatic hormone-sensitive prostate cancer (mHSPC) treated with chemohormonal therapy.^{3,4} A prospectively defined subgroup analysis in E3805

with long-term follow-up further demonstrated that the survival benefit associated with treatment was driven by men with high-volume mHSPC.⁵ Chemohormonal therapy has since become a standard option for the treatment of mHSPC with adequate performance status, particularly among men with high-volume disease.⁶

Quality of life (QOL) is of paramount importance for men with metastatic PCa because the disease is incurable and it commonly afflicts elderly men with multiple comorbid illnesses or

a borderline performance status. In the PCa population, docetaxel has an adverse event profile, with up to a 51% risk of grade 3 to 5 adverse events including neutropenic fever, peripheral neuropathy, and fluid retention.^{3,4,7} It has been hypothesized that QOL in this population is the product of the alleviation of disease-related symptoms and the introduction of treatment-related symptoms.⁸ Understanding QOL as it relates to particular therapies is critical to inform patient-provider treatment decisions.

To more clearly understand the burden of treatment, E3805 evaluated the change in QOL over 12 months to describe QOL outcomes associated with chemohormonal therapy in men with mHSPC.

METHODS

Study Oversight

The primary objective of E3805 was to assess whether chemohormonal therapy was associated with prolonged survival as compared with androgen deprivation therapy (ADT) alone in men with mHSPC.³ A patient-reported QOL assessment was performed as a secondary outcome of E3805. As detailed in a previous publication, E3805 was designed and coordinated by the Eastern Cooperative Oncology Group (ECOG; now ECOG-ACRIN) and was approved by local institutional review boards at participating institutions.³ Sanofi provided docetaxel (before progression when receiving ADT) and a grant to ECOG-ACRIN. The company did not participate in the design of the study, data collection or analysis, or manuscript preparation.

Patients

Participants were enrolled by ECOG-ACRIN, Southwest Oncology Group, Alliance for Clinical Trials in Oncology, and NRG Oncology, and the study was supported by the Clinical Trials Support Unit.³ Eligible men had an ECOG performance status of ≤ 2 without significant organ dysfunction, a pathologic diagnosis of prostate adenocarcinoma, and radiographic evidence of metastatic disease. Exposure to previous ADT for ≤ 24 months was permissible if > 12 months had passed since exposure. Men without progression when receiving ADT for mHSPC were eligible if they had started ADT within 120 days. All participants provided written informed consent.

Treatment Plan, Random Assignment, and Stratification

Men were randomly assigned to receive treatment with chemohormonal therapy (docetaxel 75 mg/m² once every 3 weeks for six cycles plus ADT; ADT+D) or with ADT alone.³ Patients were stratified by the extent of metastatic burden (high volume, defined as the presence of four or more bone metastases with one or more outside of the vertebral bodies and pelvis or visceral metastases; and low volume).³ Dose modifications to ADT were not allowed, and dose modifications for docetaxel were limited. Dose modification details are in the Data Supplement.

Data Collection

QOL surveys were administered at baseline and at 3, 6, 9, and 12 months. When necessary, staff provided neutral assistance for survey completion and prompted patients to complete incomplete items. If the patient refused, it was indicated on the questionnaire. If a patient missed a scheduled appointment, the questionnaire was completed by telephone on the appointed date or at the rescheduled appointment.

Measures

Primary outcome: Overall QOL by Functional Assessment of Cancer Therapy-Prostate. Functional Assessment of Cancer Therapy-Prostate

(FACT-P; version 4) is a patient-reported measure of QOL that contains 39 items distributed over five subscales: Physical (seven items), Social or Familial (seven items), Emotional (six items), and Functional (seven items) well-being, and additional concerns related to the Prostate Cancer Scale (12 items).⁹ Higher scores indicate better QOL. Clinically meaningful change on the FACT-P total score was considered a change of 6 to 10 points.¹⁰

Secondary outcomes: Treatment and disease-related QOL. The Trial Outcome Index (TOI) is a measure of physical and functional well-being calculated by summing the Physical and Functional Well-being subscales and the Prostate Cancer subscale.⁹ FACT-P subscales have been used in clinical trials of QOL in patients with advanced PCa to characterize specific domains.¹¹⁻¹³

The FACT-Taxane (FACT-T) Scale includes 16 items associated with adverse effects of taxane treatment, and it has excellent internal consistency, reliability, validity, and responsiveness to change.¹⁴ Higher scores indicate better QOL. A clinically meaningful difference in FACT-Taxane was a change of ≥ 1 standard error of measurement.¹⁴ The Fatigue subscale of the FACIT-F includes 13 items that assess the physical experience of fatigue.¹⁵ It exhibits strong convergent and discriminant validity, internal consistency, test-retest reliability, and sensitivity to group differences in performance status.¹⁵ Higher scores indicate better QOL. A minimal important difference (MID) for FACIT-F was considered a change of ≥ 3 points.¹⁶ The Brief Pain Inventory (BPI) Short Form includes 11 questions that assess pain intensity and interference with daily functioning.^{17,18} The reliability and validity of the BPI are well established.^{17,18} Higher scores indicate greater pain. MID was a change of ≥ 2 points for pain intensity and ≥ 0.5 of the standard deviation for pain interference.^{19,20}

In addition, we assessed QOL by PCa disease burden by comparing FACT-P total scores and subscales between treatment arms by disease burden.

Scoring Methods

FACT-P, FACT-T, and FACIT-F scores were calculated by summing all subscale items after reversing negatively stated items. If items were missing, subscale scores were prorated (we multiplied the sum of item scores by the number of total subscale items, then divided by the number of items answered) only if $\geq 50\%$ of items in the subscale were answered. The FACT-P total score was considered valid only if the FACT-P was $\geq 80\%$ complete. The BPI includes four items assessing pain intensity that were averaged to determine the average pain score. The remaining seven pain interference questions were averaged to obtain the average interference score. Score calculation required $\geq 50\%$ subscale completion. The response rate was calculated by dividing the number of patients answering any part of FACT-P by the number of patients due for an assessment. Patients who died, refused follow-up, or were lost to follow-up were not included in the denominator for the response rate.

Statistical Methods

We use descriptive statistics to characterize the patients at study entry and the distribution of QOL scores. Fisher's exact test was used to compare response rates (compliance) between arms at each time point.²¹ Differences in the distribution of QOL scores between arms and changes in QOL scores from baseline to follow-up were evaluated using the Wilcoxon rank sum test and the Wilcoxon signed rank test, respectively.²² Mixed-effect models with random intercepts for each individual were used to evaluate the differences in FACT-P total scores and TOI between the two arms over time.²³ Several baseline factors, including age (≤ 59 years ν 60 to 69 years ν ≥ 70 years), extent of disease (high volume ν low volume), local therapy (yes ν no), ECOG performance scale (PS) (0 ν 1 or 2), baseline physical well-being (≤ 20 ν 20 < physical well-being (PWB) ≤ 25 ν > 25), and baseline pain score (0 or 1 ν 2 or 3 ν ≥ 4) were included in the model and were considered to be fixed effects. The assessment time point was considered a categorical variable, and the interaction between treatment arm and assessment time was included in the model. QOL data reflect all

available data as of August 2015. All tests were two sided, and *P* values < .05 were considered significant.

RESULTS

Primary End Point: FACT-P

Between July 2006 and December 2012, 790 men enrolled in E3805 and were randomly assigned to ADT+D (n = 397) or to ADT alone (n = 393).³ Baseline characteristics were balanced between groups and have been described previously (Table 1).³ The results of the survival analysis of the study were released after a planned interim analysis in October 2013 due to meeting prespecified criteria for significance.

FACT-P surveys were completed by 90%, 86%, 83%, 78%, and 77% of participants at baseline and at 3, 6, 9, and 12 months, respectively (Table 2). Missing data rates were low, and there were similar response rates at all time points other than at 3 and 9 months, when there was a small but significantly better response rate for the ADT+D arm (Table 2). Reasons for missing data are cataloged in Appendix Table A1 (online only). A sensitivity analysis was performed using joint modeling of QOL and survival data to adjust for nonignorable

missing data, and the conclusions were unchanged (Appendix Table A2, online only).

For the primary end point, there was a statistically significant decrease in the mean FACT-P score between baseline and 3 months with ADT+D (−2.7 points, *P* < .001), but no significant change in mean FACT-P score between baseline and 3 months with ADT (−1.1 points, *P* = .4; Fig 1A). There was no significant difference in mean FACT-P score between baseline and 12 months with ADT+D (−0.7 points, *P* = .38), but the mean FACT-P score significantly decreased between baseline and 12 months with ADT (−4.2 points, *P* < .001; Appendix Table A3, online only). None of these changes met the criteria for a clinically meaningful change. A sensitivity analysis of the 25% of men reporting the greatest decline in QOL between baseline and 3 months was performed, and similar FACT-P score changes were seen.

A direct comparison of mean FACT-P total scores between treatment arms at 3 months (during chemotherapy) showed no significant difference (116.6 v 118.3, *P* = .07; Appendix Table A4, online only). In a mixed-effects model adjusted as described in Patients and Methods, the ADT+D group was associated with a significantly poorer adjusted mean FACT-P score at 3 months when compared with the ADT group (−3.09, *P* = .02; Table 3).

Table 1. Patient Demographics and Disease Characteristics by Treatment Arm

Characteristic	Arm		Total (N = 790)
	ADT+D (n = 397)	ADT (n = 393)	
Age, y, median (range)	64 (36-88)	63 (39-91)	63 (36-91)
Ethnicity			
White	344 (88.9)	330 (88.5)	674 (88.7)
Black	39 (10.1)	37 (9.9)	76 (10.0)
Asian	3 (0.8)	5 (1.3)	8 (1.1)
Native American	1 (0.3)	1(0.3)	2 (0.3)
Missing or unknown	10	20	30
ECOG PS			
0	277 (69.8)	272 (69.4)	549 (69.6)
1	114 (28.7)	115 (29.3)	229 (29.0)
2	6 (1.5)	5 (1.3)	11 (1.4)
Missing or unknown	0	1	1
Extent of disease			
High	263 (66.2)	249 (63.5)	512 (64.9)
Low	134 (33.8)	143 (36.5)	277(35.1)
Missing or unknown	0	1	1
Visceral disease (among high-volume disease patients)			
No	206 (78.3)	183 (73.5)	389 (76.0)
Yes	57 (21.7)	66 (26.5)	123 (24.0)
Local therapy type			
None	289 (72.8)	286 (73.0)	575 (72.9)
Prostatectomy	81 (20.4)	73 (18.6)	154 (19.5)
Definitive RT	27 (6.8)	33 (8.4)	60 (7.6)
Missing or unknown	0	1	1
PSA before ADT			
No.	392	392	784
Nanogram/milliliter, median (range)	50.9 (0.2-8,540.1)	52.1 (0.1-8,056.0)	51.4(0.1-8,540.1)
Patients who started ADT before random assignment			
No.	344	340	684
Time from start of ADT to random assignment, mo, median (range)*	1.2 (0.03-3.9)	1.3 (0.03-3.9)	1.2 (0.03-3.9)
FACT-P total at baseline			
No.	360	346	706
Mean (SD)	119.4 (20.1)	118.7 (22.1)	119.0 (21,1)

NOTE. Data are presented as No. (%) unless indicated otherwise.

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Scale; FACT-P, Functional Assessment of Cancer Therapy-Prostate; PSA, prostate-specific antigen; RT, radiation therapy.

*Among patients who started ADT before random assignment.

Table 2. FACT-P Compliance by Treatment Arm

Treatment Arm	Response Rate at Assessment Time Points				
	Baseline	3 Months	6 Months	9 Months	12 Months
Total	90.3 (713 of 790)	86.4 (665 of 770)	83.4 (635 of 761)	78.3 (583 of 745)	77.0 (555 of 721)
ADT+D	92.2 (366 of 397)	89.9 (348 of 387)	83.8 (321 of 383)	81.3 (305 of 375)	77.5 (285 of 368)
ADT alone	88.3 (347 of 393)	82.8 (317 of 383)	83.1 (314 of 378)	75.1 (278 of 370)	76.5 (270 of 353)
<i>P</i> *	.07	.005	.85	.04	.79

NOTE. Data are presented as % (No. patients with FACT-P submission out of the number of patients with quality of life [QOL] assessment due at each time point). Patients who answered any part of the FACT-P questionnaire were considered to have submitted a FACT-P assessment for a given time point; patients who died, refused follow-up, or were lost to follow-up before a given time point were not considered to have a QOL assessment due for that time point.

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; FACT-P, Functional Assessment of Cancer Therapy-Prostate.

*Fisher's exact test was used to compare the response rates between the two arms at each time point.

Conversely, at 12 months, ADT+D was associated with a higher mean adjusted FACT-P score when compared with that of ADT (2.85, *P* = .04; Table 3). Differences between arms did not meet the criteria for a clinically meaningful difference at any time point.

Secondary End Points

FACT-P subscales. We evaluated the TOI and FACT-P subscales to determine the effect of treatment and disease on specific

domains of QOL (Appendix Table A4). At 3 months, mean TOI and the physical and functional well-being subscales were significantly lower with ADT+D than with ADT alone (TOI, 74.9 v 77.6, *P* = .003), but they were similar at all other time points. In a mixed-effects model adjusted as described in Patients and Methods, ADT+D was associated with significantly lower TOI scores than was ADT at 3 months only (−3.44, *P* < .001; Appendix Table A5, online only).

FACT-Taxane. We used the FACT-Taxane to assess the treatment effect within and between arms over time. FACT-Taxane

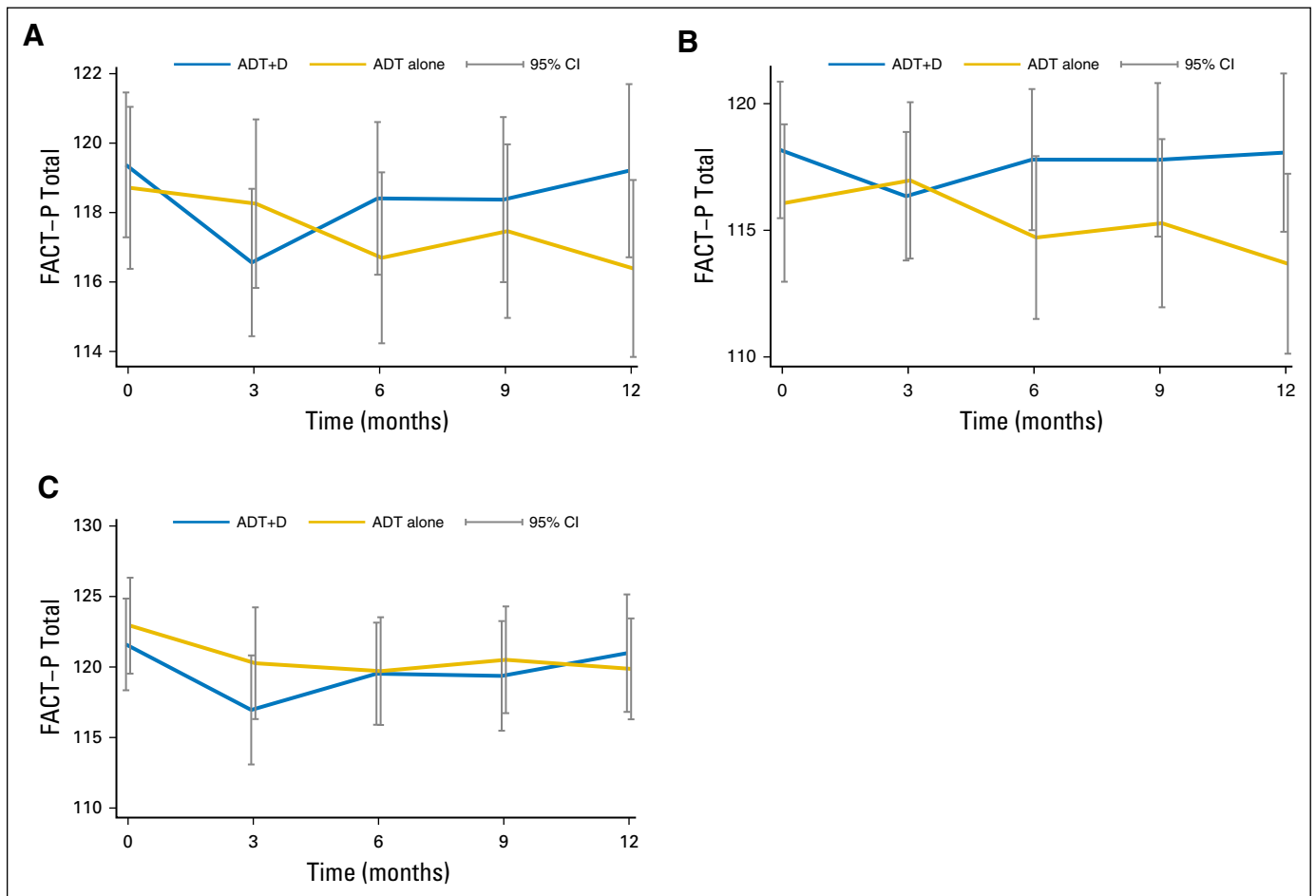


Fig 1. Comparison of Functional Assessment of Cancer Therapy-Prostate (FACT-P) scores over time between the docetaxel and androgen deprivation therapy (ADT+D) and androgen deprivation therapy (ADT) arms, including (A) FACT-P scores for the entire population; (B) FACT-P scores for high-volume patients; and (C) FACT-P scores for low-volume patients. Clinically meaningful change on the FACT-P total score was considered a change of 6 to 10 points.

Table 3. Mixed-Effects Model* for FACT-P Total Score

Time Point	Difference between ADT+D and ADT Alone†		
	Estimate	SE	P
Baseline	-1.00	1.28	.43
3 months	-3.09	1.32	.02
6 months	0.90	1.34	.50
9 months	0.29	1.37	.84
12 months	2.85	1.39	.04

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Scale; FACT-P, Functional Assessment of Cancer Therapy-Prostate; PWB, physical well-being.

*With adjustment for age (≤ 59 years ν 60 to 69 years ν ≥ 70 years), extent of disease (high ν low), local therapy (yes ν no), ECOG PS (0 ν 1 or 2), baseline physical well-being (≤ 20 ν 20 < PWB ≤ 25 ν > 25), and baseline pain score (0 or 1 ν 2 or 3 ν ≥ 4); clinically meaningful change on the FACT-P total score was considered a change of 6 to 10 points.

†ADT+D score minus ADT alone score; higher scores represent better quality of life.

scores were significantly lower for ADT+D than for ADT at all time points after baseline (Appendix Table A6, online only). FACT-Taxane scores declined significantly from baseline in both treatment arms at all time points (Fig 2A). No differences between groups or changes over time met the criteria for MID.

FACIT-Fatigue. Mean scores for the FACIT-Fatigue were similar between arms at baseline and at all subsequent time points, with the exception of 3 months (36.1 ν 40.4 for the ADT+D and ADT arms at 3 months, respectively; $P < .001$; Appendix Table A6; Fig 2B). At 3 months, both the change in FACIT-Fatigue score from baseline with ADT+D and the difference between arms met the criteria for MID.

BPI. There was no significant difference between arms in BPI pain intensity or interference scores at any time point (Figs 2C and 2D). Pain increased slightly over time in both groups but did not meet the minimal clinically important difference at any time point (Appendix Table A6).

High- Versus Low-Volume Disease

We assessed overall QOL between arms and over time by comparing FACT-P scores by disease burden (Figs 1B and 1C). There was no significant difference in mean FACT-P scores between treatment arms within the high- or low-volume groups (Appendix Table A7, online only). Among high-volume patients, there was no significant change in mean FACT-P score between baseline and any time point with ADT+D (Appendix Table A8, online only). Among high-volume patients receiving ADT alone, the mean FACT-P score at 12 months was significantly lower than

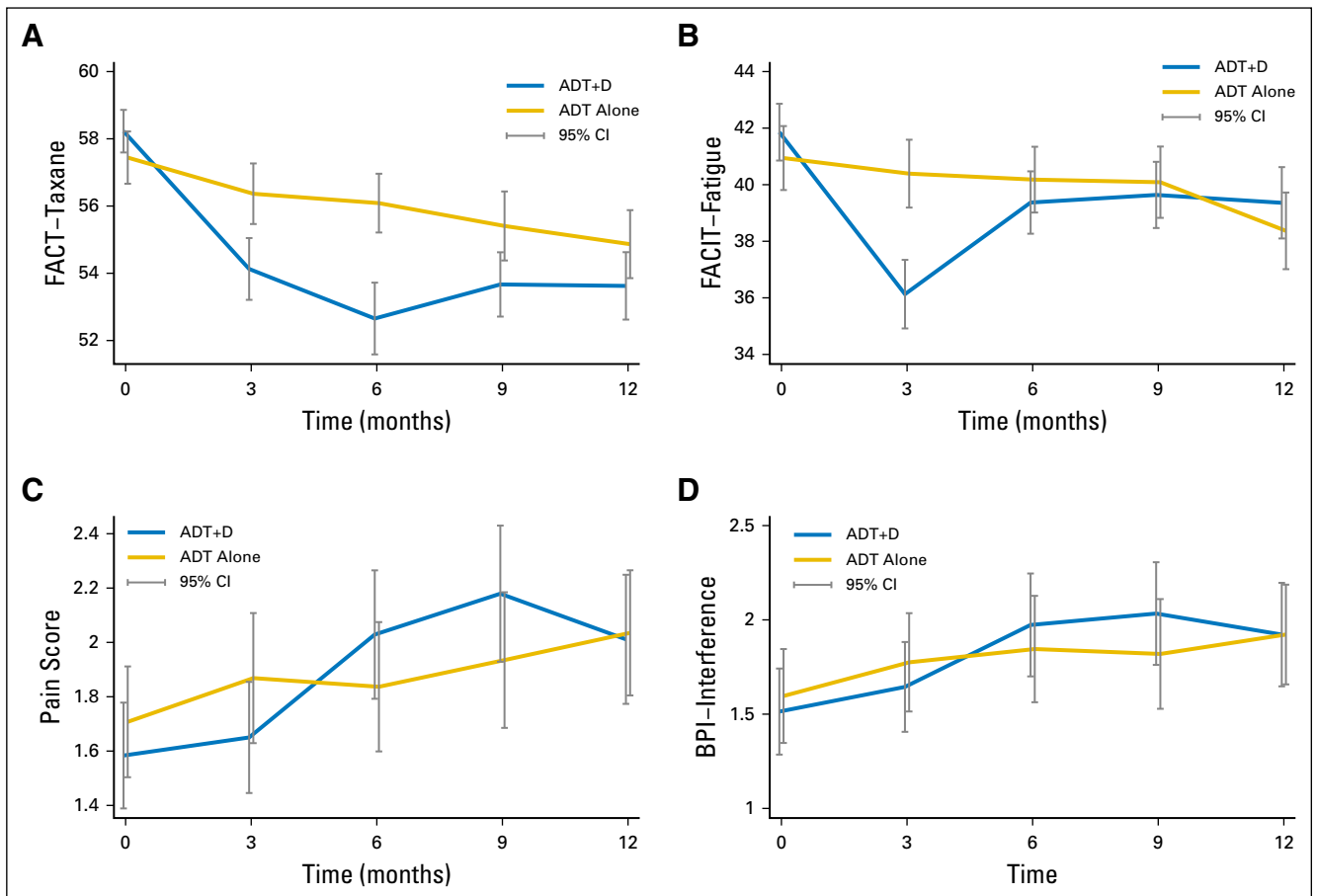


Fig 2. Treatment-associated and disease-associated symptoms over time between the docetaxel and androgen deprivation therapy (ADT+D) and androgen deprivation therapy (ADT) arms, including (A) the Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) subscale; (B) the FACIT-Fatigue subscale; (C) the Brief Pain Inventory (BPI) pain subscale; and (D) the BPI interference subscale.

at baseline (-3.9 , $P = .04$; Appendix Table A8). Among ADT+D low-volume patients, the mean FACT-P score decreased significantly between baseline and 3 months (-5.3 , $P < .001$), but scores did not differ from baseline at 6, 9, or 12 months (Appendix Table A8). Among ADT low-volume patients, the mean FACT-P score was significantly lower than at baseline at all time points (Appendix Table A8).

DISCUSSION

We assessed QOL over time in men treated with ADT+D or ADT alone to assess the benefit-to-harm ratio of chemohormonal therapy for mHSPC. Our data suggest that overall QOL declines for men in the ADT+D arm at 3 months, but improves to nearly baseline levels by 12 months. As we might expect, ADT+D was associated with poorer physical and functional QOL at 3 months, presumably because of treatment effects, but differences between the groups resolved by 6 months. There was a gradual decline in QOL over time in the ADT-alone arm, consistent with findings in other metastatic PCa populations on effective hormonal therapy.²⁴ Treatment burden as reflected by the FACT-Taxane demonstrated significantly poorer scores among men treated with ADT+D than with ADT alone at all time points after baseline. Fatigue was significantly greater in the ADT+D arm when compared with ADT only at 3 months, and pain intensity and interference were similar between arms at all time points. Although the identified differences were significantly different statistically, changes in QOL did not meet the criteria for clinically meaningful change by any measure.

When using the findings from this study in clinical decisions, individual patient characteristics, specific comorbidities, performance status, and other psychosocial factors that may contribute to a patient's tolerance of treatment and treatment experience should be considered. This patient population represents a slightly younger age than the average age of men with PCa (median age of 63 years in the E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer [CHAARTED] v median age of 66 years in men with PCa), and a majority have high-volume metastatic disease (64.9% overall) and an ECOG performance status of 0 (nearly 70%) or 1 (approximately 29%).² The findings may be less applicable to older, frailer men and should be considered in concert with the updated analysis that fails to find a survival advantage from chemohormonal therapy in men with low-volume disease.⁵ Clinicians should also consider QOL data from treatment with ADT, abiraterone acetate, and prednisone until progression in the mHSPC setting.^{26,27} Abiraterone acetate and chemohormonal therapy may confer similar survival benefits in this patient population, and considerations of differences in the adverse effect profile of long-term abiraterone acetate and prednisone are likely to be distinct from those associated with six cycles of docetaxel and ongoing ADT.²⁸

Although patient-reported outcomes are commonly incorporated into PCa clinical trials for localized disease, they have been less consistently included in studies of advanced PCa.²⁹⁻³¹ A challenge for the field has been a lack of consistency across studies in the QOL instruments included in trials of advanced

PCa, making comparisons of different treatment approaches less than straightforward. Treatment trials in men with metastatic PCa have not consistently demonstrated a significant change in global measures of QOL.^{8,32} To address this, we included an analysis of FACT-P subscales and additional QOL instruments and compared QOL between and within arms, to provide a more nuanced description of QOL than could be provided by relying on a single instrument alone.

To our knowledge, this prospective, randomized study is the first QOL comparison between chemohormonal therapy and ADT alone, and the first longitudinal analysis of these treatments. As clinicians determine whether to guide decisions by overall survival data in CHAARTED, LATITUDE, and STAMPEDE, by CHAARTED subgroup analysis data for high- versus low-volume mHSPC, or by QOL data from these studies, this QOL analysis will enable them to consider the QOL effects of these treatments in the shared decision-making process.^{3-5,26,27,33} This study is limited in that the analysis cannot definitively attribute detriments in QOL to treatment or disease progression with the included instruments, although FACT-T changes are likely more specific to treatment than to disease progression. However, to the best of our knowledge, it is the most comprehensive study of the QOL to date in this patient population. The longitudinal data demonstrating an improvement in overall QOL at 12 months in the chemohormonal arm suggests that the physical and functional deficits present at the 3-month time point are reversible short-term deficits. Because participants were not blinded to treatment, it is also possible that the knowledge of having received an additional treatment (chemotherapy) might have affected their perspective and QOL reports, although this was likely reduced by the comprehensive assessment of diverse aspects of QOL (physical, functional, prostate cancer [PCa] specific, and so forth). In addition, we report QOL differences that were statistically significant as reported by patients, but we cannot define within this study how clinically meaningful they were to patients. Separate work has defined clinically meaningful change in the QOL measures used in various clinical settings.^{10,14,16,19,20} Clinically meaningful differences can be calculated by multiple methods, including anchoring to patient-reported global rating scales or objective physician-designated clinical measures (eg, performance status), or on the basis of standard deviation within a cohort.^{34,35} Although the differences in QOL in this study did not meet previously defined MID levels, these changes and differences were rigorously collected from patients during treatment and are a valid patient-reported contribution to consider when choosing treatment of mHSPC. Finally, we acknowledge that this study does not report on late effects from treatment that may be important in clinical decision making.

This analysis compares the QOL of men receiving ADT+D and ADT alone, assesses QOL over time with multiple instruments, and evaluates QOL by disease burden. Men treated with ADT+D had poorer QOL outcomes than did men treated with ADT alone at 3 months while undergoing chemotherapy. However, by 12 months, ADT+D patients reported statistically superior overall QOL outcomes by FACT-P. These findings must be considered in the context of the population assessed and in the context of a simultaneously reported subgroup analysis that failed to find an improvement in overall survival in

men with low-volume mHSPC treated with ADT+D. Clinicians treating men with mHSPC who are fit enough to receive chemotherapy should consider that ADT+D is associated with both stable to improved QOL at 12 months and greater longevity than ADT alone.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Christopher J. Sweeney, David F. Jarrard, Benjamin A. Gartrell, Michael A. Carducci, Linda J. Patrick-Miller
Provision of study materials or patients: Michael A. Carducci
Collection and assembly of data: Alicia K. Morgans, Yu-Hui Chen, Christopher J. Sweeney, Benjamin A. Gartrell, Michael A. Carducci, Maha Hussain
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

Alicia K. Morgans, Maha Hussain, and David Cella, Northwestern University Feinberg School of Medicine, Chicago, IL; Yu-Hui Chen and Christopher J. Sweeney, Dana Farber Cancer Institute, Boston, MA; David F. Jarrard, University of Wisconsin Hospital and Clinics, Madison, WI; Elizabeth R. Plimack, Fox Chase Cancer Center, Philadelphia, PA; Elizabeth R. Plimack and Benjamin A. Gartrell,

Montefiore Medical Center, Bronx, NY; **Michael A. Carducci**, Johns Hopkins University, Baltimore, MD; **Jorge A. Garcia**, Cleveland Clinic, Cleveland, OH; **Robert S. DiPaola**, University of Kentucky College of Medicine, Lexington, KY; and **Linda J. Patrick-Miller**, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer

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Alicia K. Morgans

Honoraria: Genentech, Janssen Pharmaceuticals

Consulting or Advisory Role: Genentech, AstraZeneca, Sanofi

Travel, Accommodations, Expenses: Genentech, AstraZeneca, Janssen Pharmaceuticals

Yu-Hui Chen

Employment: Constellation Pharmaceuticals (I)

Christopher J. Sweeney

Stock or Other Ownership: Leuchemix

Consulting or Advisory Role: Sanofi, Janssen Biotech, Astellas Pharma, Bayer AG, Genentech/Roche, AstraZeneca, Pfizer

Research Funding: Janssen Biotech (Inst), Astellas Pharma (Inst), Sanofi (Inst), Bayer AG (Inst), Sotio (Inst)

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David F. Jarrard

No relationship to disclose

Elizabeth R. Plimack

Consulting or Advisory Role: AstraZeneca/MedImmune, Bristol-Myers Squibb, Clovis Oncology, Exelixis, AstraZeneca/MedImmune, Synergene, Acceleron Pharma, Eli Lilly, Horizon Pharma, Pfizer, Inovio Biomedical

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Benjamin A. Gartrell

Consulting or Advisory Role: Pfizer, Exelixis, Bayer AG

Michael A. Carducci

Consulting or Advisory Role: Astellas Pharma, Churchill Pharmaceuticals, Abbvie, Roche/Genentech, Pfizer

Research Funding: Bristol-Myers Squibb (Inst), Pfizer (Inst), AstraZeneca (Inst), Gilead Sciences (Inst)

Maha Hussain

Honoraria: Onclive, Sanofi

Research Funding: Genentech (Inst), Pfizer (Inst), PCCTC (Inst), Bayer AG (Inst), AstraZeneca (Inst)

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Travel, Accommodations, Expenses: Sanofi

Jorge A. Garcia

Honoraria: Astellas Pharma, Sanofi, Bayer AG, Pfizer

Consulting or Advisory Role: Sanofi, Pfizer, Bayer AG, Medivation

Speakers' Bureau: Bayer AG, Sanofi, Medivation/Astellas Pharma

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David Cella

No relationship to disclose

Robert S. DiPaola

No relationship to disclose

Linda J. Patrick-Miller

No relationship to disclose

Appendix

Descriptive statistics were used to characterize reasons for Functional Assessment of Cancer Therapy-Prostate (FACT-P) noncompliance and the distribution of quality of life (QOL) scores. Differences in the distribution of QOL scores between arms and changes in QOL scores from baseline to follow-up were evaluated using the Wilcoxon rank sum test and the Wilcoxon signed rank test, respectively.²² Distribution of FACT-P total scores and changes from baseline were also presented by volume of disease and among the 25% of patients with the greatest alterations at 3 months. Mixed-effect models with random intercepts for each individual were used to evaluate the differences in Trial Outcome Index score between the two arms over time.²³ Several baseline factors, including age (≤ 59 years ν 60 to 69 years ν ≥ 70 years), extent of disease (high volume ν low volume), local therapy (yes ν no), Eastern Cooperative Oncology Group PS (0 ν 1 or 2), baseline physical well-being (≤ 20 ν $20 < \text{PWB} \leq 25$ ν > 25) and baseline pain score (0 or 1 ν 2 or 3 ν ≥ 4) were included in the model and were considered to be fixed effects. Assessment time point was considered a categorical variable, and the interaction between treatment arm and assessment time was included in the model. A joint model (Schluchter MD: Methods for the analysis of informatively censored longitudinal data. Stat Med 11(14-15):1861-1870, 1992) of longitudinal FACT-P measurements and survival data was performed to explore the trend of QOL changes over time. The mean slope of FACT-P scores over time was estimated for each arm, and bootstrap standard errors were computed. QOL data reflect all available data as of August 2015. All tests were two sided, and P values $< .05$ were considered significant.

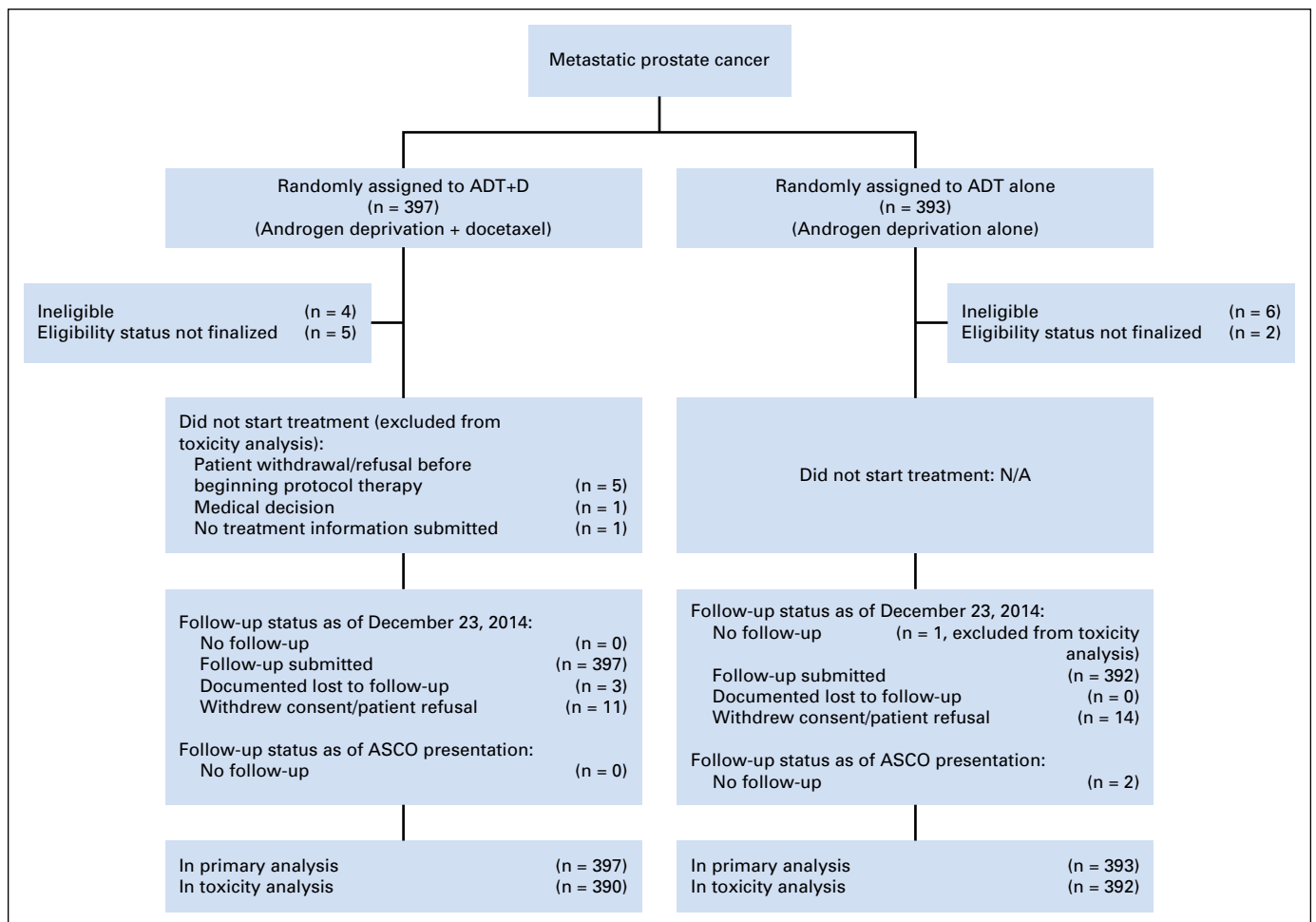


Fig A1. CONSORT diagram. ADT+D, docetaxel and androgen deprivation therapy; ADT, androgen deprivation therapy.

Table A1. Reasons for FACT-P Noncompliance by Arm Over Time*

Reason	Baseline		3 Months		6 Months		9 Months		12 Months	
	ADT+D	ADT	ADT+D	ADT	ADT+D	ADT	ADT+D	ADT	ADT+D	ADT
Patient refusal	5	6	6	7	5	10	7	14	8	10
Unable to accommodate disability or language needs	0	0	0	0	0	0	0	0	0	0
Patient did not show up in clinic or office	0	1	1	7	1	5	4	3	4	5
Staff unavailable	0	1	0	2	1	3	1	4	2	2
Patient not given form by staff	2	12	12	21	24	16	25	30	27	22
Patient too ill	0	0	1	0	1	2	1	0	0	1
Patient expired	0	0	0	0	0	0	0	2†	0	1‡
Assessment not required per protocol	0	0	0	0	0	1	0	1	1	1
Staff thought patient too ill	0	0	0	2	2	0	1	0	1	0
Patient did not show up in clinic or patient too ill	0	0	0	0	0	1	0	0	0	0
Staff unavailable or patient not given form by staff	0	0	0	0	1	1	2	1	0	0
Patient refusal or patient did not show up in clinic	0	0	0	0	0	0	0	0	1	1
Patient too ill or staff thought patient too ill	0	0	0	0	0	0	0	0	1	0
Staff thought patient too ill or patient not given form by staff	0	0	0	0	0	0	0	0	0	1
Patient did not show up in clinic or patient not given form by staff or patient too ill or staff thought patient too ill	0	0	0	0	0	1	0	0	0	0
Other	0	2	2	6	7	3	4	8	6	13
Unknown or missing	24	24	17	21	20	21	25	29	32	26
Total	31	46	39	66	62	64	70	92	83	83

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; FACT-P, Functional Assessment of Cancer Therapy-Prostate.
 *Research staff submitted one reason for why the form was not completed in all but a few instances in which multiple reasons were submitted (these are listed in the latter half of the table).

†Two patients died shortly after 9 months from random assignment. They were alive at the FACT-P assessment time point (month 9), so forms are considered due for the 9-month evaluation.

‡One patient died shortly after 12 months from random assignment. He was alive at the FACT-P assessment time point (month 12), so forms are considered due for the 12-month evaluation.

Table A2. Estimation of Mean Slope of FACT-P Score in a Joint Model of QOL Assessments and Survival Data

Treatment Arm	Baseline to 3 Months		3 Months to 12 Months	
	Slope*	SE†	Slope*	SE†
ADT+D	-0.7	1.5	0.9	1.5
ADT alone	0.6	0.5	-0.6	0.2

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; FACT-P, Functional Assessment of Cancer Therapy-Prostate; QOL, quality of life.

*FACT-P score change/month.

†Bootstrap standard error.

Table A3. Distributions of Changes from Baseline to Follow-Up for FACT-P Total Scores*

Change	ADT+D						ADT Alone					
	No.	Mean	SE	Median	Range†	P†	No.	Mean	SE	Median	Range	P
From baseline to 3 months	334	-2.7	0.9	-3.0	-53.2-59.5	.0009	299	-1.1	1.0	0.0	-63.0-61.7	.4000
From baseline to 6 months	307	-0.7	0.8	-1.0	-45.0-63.0	.2100	294	-2.5	0.9	-1.0	-69.4-64.0	.0070
From baseline to 9 months	293	-1.4	1.0	-0.4	-55.3-58.8	.2500	263	-2.6	1.0	-1.3	-82.2-49.3	.0100
From baseline to 12 months	269	-0.7	1.1	-1.6	-82.3-72.0	.3800	253	-4.2	1.1	-3.8	-65.4-51.0	.0004

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; FACT-P, Functional Assessment of Cancer Therapy-Prostate.
 *Total score = physical + social/family + emotional + functional + prostate cancer additional concerns; clinically meaningful change on the FACT-P total score was considered a change of 6 to 10 points.

†Wilcoxon signed rank test comparing follow-up scores and baseline scores in each arm.

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Table A4. Distribution of FACT-P Total Scores and Subscale Scores Over Time by Arm

	ADT+D					ADT alone					P* (rank sum)
	No.	Mean	SE	Median	Range	No.	Mean	SE	Median	Range	
Total score†											
Baseline	360	119.4	1.1	123.1	47-156	346	118.7	1.2	123.5	43.7-153.9	.9100
3 months	344	116.6	1.1	118.0	39.6-155	313	118.3	1.2	123.8	45-155	.0700
6 months	318	118.4	1.1	121.0	49-156	310	116.7	1.3	120.5	44.0-156	.5200
9 months	304	118.4	1.2	122.0	40-154.9	273	117.5	1.3	123.0	29.8-154.8	.7000
12 months	279	119.2	1.3	122.8	52-156	265	116.4	1.3	120.0	42.8-156	.0900
TOI‡											
Baseline	363	78.7	0.8	82.0	25-104	347	77.8	0.9	82.4	15-104	.9200
3 months	345	74.9	0.8	76.0	23.6-103	314	77.6	1.0	82.5	16.4-104	.0030
6 months	319	76.9	0.9	79.0	19-104	312	76.3	1.0	80.0	20.8-104	.9600
9 months	305	76.8	0.9	80.0	10-104	275	76.8	1.0	81.0	23-102.8	.8100
12 months	279	77.4	1.0	80.0	18-104	266	75.7	1.0	78.0	20.4-104	.2100
Physical											
Baseline	366	24.1	0.2	26.0	7-28	347	23.7	0.3	25.0	0-28	.3900
3 months	347	21.4	0.3	23.0	5-28	315	23.0	0.3	25.0	0-28	<.0001
6 months	320	22.8	0.2	23.7	4-28	313	23.0	0.3	25.0	4-28	.1200
9 months	305	23.0	0.3	24.0	2-28	276	22.9	0.3	25.0	5-28	.7100
12 months	283	22.7	0.3	24.0	2-28	269	22.4	0.3	24.0	1-28	.4400
Social/family											
Baseline	365	22.9	0.2	24.0	0-28	347	22.7	0.3	24.0	0-28	.4000
3 months	346	22.6	0.2	23.3	0-28	314	22.4	0.2	23.3	7-28	.3800
6 months	320	22.6	0.3	24.0	0-28	313	21.9	0.3	23.0	0-28	.0600
9 months	304	22.7	0.3	24.0	0-28	275	22.2	0.3	23.3	0-28	.0900
12 months	283	22.7	0.3	24.0	0-28	268	22.1	0.3	23.0	3-28	.0700
Emotional											
Baseline	363	17.8	0.2	18.0	2-24	346	18.1	0.2	19.0	3-24	.1000
3 months	347	19.0	0.2	20.0	5-24	317	18.4	0.2	19.0	0-24	.0800
6 months	318	18.9	0.2	20.0	6-24	313	18.3	0.2	19.0	6-24	.0700
9 months	305	18.9	0.2	20.0	0-24	275	18.5	0.2	19.0	1-24	.1300
12 months	281	19.1	0.3	20.0	2-24	268	18.5	0.3	19.6	5-24	.0600
Functional											
Baseline	363	20.4	0.3	21.0	0-28	347	20.1	0.3	21.0	0-28	.5800
3 months	347	19.1	0.3	19.0	3-28	317	20.4	0.3	21.0	2-28	.0030
6 months	319	19.9	0.3	20.0	2-28	313	19.7	0.4	21.0	0-28	.9000
9 months	305	20.1	0.3	21.0	3-28	276	20.1	0.4	21.0	3-28	.8900
12 months	281	20.3	0.4	21.0	4-28	266	20.2	0.3	21.0	2-28	.6400
PCa§											
Baseline	366	34.2	0.4	36.0	7-48	347	34.0	0.4	36.0	10-48	.9100
3 months	346	34.4	0.4	35.0	7-48	316	34.0	0.4	36.0	8.4-48	.7500
6 months	320	34.2	0.4	35.0	3-48	313	33.6	0.4	34.9	9.8-48	.3200
9 months	305	33.7	0.4	35.0	3-48	277	33.8	0.4	35.0	8-48	.8100
12 months	282	34.3	0.4	35.0	11-48	268	33.0	0.5	33.0	12-48	.0400

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; FACT-P, Functional Assessment of Cancer Therapy-Prostate; PCa, prostate cancer; TOI, Trial Outcome Index.

*Wilcoxon rank sum test between the two arms for each subscale at each time point.

†Total score = physical + social/family + emotional + functional + PCa additional concerns; clinically meaningful change on the FACT-P total score was considered a change of 6 to 10 points.

‡TOI = physical + functional + prostate cancer additional concerns.

§PCa-specific concerns subscale.

Table A5. Mixed-Effects Model* for TOI Score

Time Point	Difference Between ADT+D and ADT Alone†		
	Estimate	SE	P
Baseline	-0.55	0.96	.5700
3 months	-3.44	1.00	.0005
6 months	0.22	1.01	.8300
9 months	-0.40	1.04	.7000
12 months	1.75	1.06	.1000

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; TOI, Trial Outcome Index.
 *With adjustment for age (≤ 59 years v 60 to 69 years v ≥ 70 years), extent of disease (high v low), local therapy (yes v no), Eastern Cooperative Oncology Group Performance Scale (0 v 1 or 2), baseline physical well-being (≤ 20 v $20 <$ PWB ≤ 25 v > 25), and baseline pain score (0 or 1 v 2 or 3 v ≥ 4).
 †ADT+D score minus ADT alone score.

Table A6. Distribution of Additional QOL Scores Over Time by Treatment Arm, Including FACT-Taxane, FACIT-Fatigue, and Brief Pain Index Pain and Interference Scores

	Arm A (ADT+D)			Arm B (ADT alone)			P*
	No.	Mean	SD	No.	Mean	SD	
FACT-Taxane†							
Baseline	361	58.2	6.1	346	57.4	7.4	.6800
3 months	345	54.1	8.7	312	56.4	8.1	<.0001
6 months	318	52.7	9.7	305	56.1	7.8	<.0001
9 months	306	53.7	8.5	273	55.4	8.6	.0030
12 months	282	53.6	8.6	266	54.9	8.4	.0300
FACIT-Fatigue‡							
Baseline	361	41.9	9.7	346	40.9	10.7	.4400
3 months	339	36.1	11.3	312	40.4	10.8	<.0001
6 months	318	39.4	10.0	308	40.2	10.4	.1400
9 months	301	39.6	10.3	277	40.1	10.7	.3400
12 months	280	39.4	10.7	265	38.4	11.2	.3200
Pain scores§							
Baseline	337	1.6	1.8	326	1.7	1.9	.5000
3 months	323	1.7	1.9	298	1.9	2.1	.2900
6 months	298	2.0	2.1	298	1.8	2.1	.1200
9 months	290	2.2	2.2	265	1.9	2.1	.1800
12 months	272	2.0	2.0	261	2.0	1.9	.6700
Interference 							
Baseline	339	1.5	2.1	317	1.6	2.3	.8500
3 months	316	1.6	2.2	290	1.8	2.3	.6000
6 months	292	2.0	2.4	289	1.8	2.4	.1500
9 months	288	2.0	2.3	258	1.8	2.4	.0800
12 months	263	1.9	2.3	257	1.9	2.2	.8400

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-Taxane, Functional Assessment of Cancer Therapy-Taxane; QOL, quality of life.
 *Wilcoxon rank sum test between the two arms at each time point.
 †Clinically meaningful important difference in FACT-Taxane was a change of ≥ 1 standard error of measurement.
 ‡Minimal important difference for FACIT-Fatigue was considered a change of ≥ 3 points.
 §Average score of the four pain questions (worst, least, average, and now), where 0 = no pain and 10 = pain as bad as you can imagine; minimal important difference was a change of ≥ 2 points for pain intensity.
 ||Average score of the seven interference questions, where 0 = does not interfere and 10 = completely interferes; minimal important difference was ≥ 0.5 of the standard deviation for pain interference.

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Table A7. Distribution of FACT-P Total Score* Over Time by Arm and Disease Volume

Time Point	ADT+D					ADT alone					P† (rank sum)	
	N	Mean	SE	Median	Range	N	Mean	SE	Median	Range		
High volume												
Baseline‡	234	118.2	1.4	121.5	47-156	213	116.1	1.6	120.8	43.7-153.9	.48	
3 months	223	116.3	1.3	117	39.6-155	191	117.0	1.6	122.0	57.4-154	.35	
6 months	205	117.8	1.4	120	49-156	187	114.7	1.6	117.0	44.0-156	.21	
9 months	191	117.8	1.5	121	40-154.9	159	115.3	1.7	120.0	29.8-154.8	.30	
12 months	170	118.0	1.6	120.9	52-156	149	113.7	1.8	117.0	42.8-156	.10	
Low volume												
Baseline‡	126	121.6	1.6	126	59-152.8	133	122.9	1.7	128.0	64-152	.30	
3 months	121	117.0	2.0	121	56-151	122	120.3	2.0	128.5	45-155	.12	
6 months	113	119.5	1.8	122	59-151	123	119.7	1.9	126.0	55.5-152	.70	
9 months	113	119.4	2.0	123	52-152	114	120.5	1.9	125.9	65.3-149.7	.63	
12 months	109	121.0	2.1	125	54.5-151	116	120.0	1.8	121.0	57.4-152	.36	

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; FACT-P, Functional Assessment of Cancer Therapy-Prostate. *Total score = physical + social/family + emotional + functional + prostate cancer additional concerns; clinically meaningful change on the FACT-P total score was considered a change of 6 to 10 points.

†Wilcoxon rank sum test between the two arms for each subscale at each time point.

‡Wilcoxon rank sum test was used to compare baseline FACT-P total score between high-volume and low-volume patients. Patients with low-volume disease had higher FACT-P scores than did high-volume patients at baseline ($P = .003$).

Table A8. Distributions of Changes From Baseline to Follow-Up for FACT-P Total Scores by Arm and Disease Volume*

Change	ADT+D						ADT alone					
	No.	Mean	SE	Median	Range	P†	No.	Mean	SE	Median	Range	P†
High volume												
From baseline to 3 months	215	-1.30	1.1	-1.20	-53.2-59.5	.1300	183	0.41	1.4	0.33	-63.0-61.7	.560
From baseline to 6 months	197	0.03	1.1	-0.70	-45.0-47.0	.8100	177	-1.50	1.3	-1.0	-69.4-64.0	.310
From baseline to 9 months	183	-1.00	1.3	0.00	-55.3-45.0	.5100	152	-2.10	1.4	-1.4	-82.2-49.3	.130
From baseline to 12 months	162	-0.30	1.4	-2.75	-46.0-72.0	.3700	143	-3.9	1.6	-3.2	-65.4-51.0	.040
Low volume												
From baseline to 3 months	119	-5.30	1.4	-4.00	-51.0-47.8	.0003	116	-3.5	1.3	-1.0	-56.0-33.8	.020
From baseline to 6 months	110	-2.00	1.3	-2.00	-38.0-63.0	.0700	117	-4.1	1.2	-2.0	-43.0-30.0	.002
From baseline to 9 months	110	-2.00	1.5	-1.00	-50.0-58.8	.3400	111	-3.2	1.2	-1.3	-44.0-27.5	.040
From baseline to 12 months	107	-1.20	1.7	-1.00	-82.3-53.0	.8400	110	-4.6	1.4	-4.0	-49.7-37.0	.001

Abbreviations: ADT, androgen deprivation therapy; ADT+D, docetaxel and androgen deprivation therapy; FACT-P, Functional Assessment of Cancer Therapy-Prostate. *Total score = physical + social/family + emotional + functional + prostate cancer additional concerns; clinically meaningful change on the FACT-P total score was considered a change of 6 to 10 points.

†Wilcoxon signed rank test comparing follow-up scores and baseline scores in each arm.