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Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomized clinical trial

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Background: To present longitudinal changes in Functional Assessment of Cancer Therapy-Prostate (FACT-P) scores during 25-week treatment with enzalutamide or placebo in men with progressive metastatic castration-resistant prostate cancer (mCRPC) after chemotherapy in the AFFIRM trial.

Patients and methods: Patients were randomly assigned to enzalutamide 160 mg/day or placebo. FACT-P was completed before randomization, at weeks 13, 17, 21, and 25, and every 12 weeks thereafter while on study treatment. Longitudinal changes in FACT-P scores from baseline to 25 weeks were analyzed using a mixed effects model for repeated measures (MMRM), with a pattern mixture model (PMM) applied as secondary analysis to address non-ignorable missing data. Cumulative distribution function (CDF) plots were generated and different methodological approaches and models for handling missing data were applied. Due to the exploratory nature of the analyses, adjustments for multiple comparisons were not made. AFFIRM is registered with ClinicalTrials.gov, number NCT00974311.

Results: The intention-to-treat FACT-P population included 938 patients (enzalutamide, $n = 674$; placebo $n = 264$) with evaluable FACT-P assessments at baseline and ≥1 post-baseline assessment. After 25 weeks, the mean FACT-P total score decreased by 1.52 points with enzalutamide compared with 13.73 points with placebo ($P < 0.001$). In addition, significant treatment differences at week 25 favoring enzalutamide were evident for all FACT-P subscales and indices, whether analyzed by MMRM or PMM. CDF plots revealed differences favoring enzalutamide compared with placebo across the full range of possible response levels for FACT-P total and all disease- and symptom-specific subscales/indices.

Conclusion: In men with progressive mCRPC after docetaxel-based chemotherapy, enzalutamide is superior to placebo in health-related quality-of-life outcomes, regardless of analysis model or threshold selected for meaningful response.

Clinical trial number: NCT00974311.

Key words: metastatic castration-resistant prostate cancer, patient-reported outcomes, health-related quality of life

introduction

Contemporary phase III clinical trials for anti-cancer drugs are designed primarily to test survival- or imaging-based outcomes. Patient-reported outcomes, which provide insight into the impact of treatment on patients' quality of life are often omitted or included only as secondary or exploratory analyses. A recent systematic review of clinical trials of approved prostate cancer therapies showed that only 17% of trials included patient-reported outcomes or health-related quality-of-life (HRQoL) measures [1], yet this type of information is highly relevant to patients with advanced prostate cancer. The increasing use of HRQoL data has prompted guidance from industry regulators [2] and calls from opinion leaders [3] for a more patient-oriented approach to drug development in oncology.

In the randomized phase III AFFIRM study, enzalutamide, an oral androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway, significantly prolonged overall survival compared with placebo in men with metastatic castration-resistant prostate cancer (mCRPC) after chemotherapy [4]. The AFFIRM study also included secondary end points involving patient-reported outcomes on HRQoL, reported using tools such as the Functional Assessment of

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Cancer Therapy-Prostate (FACT-P) [4, 5]. The FACT-P is a reliable and validated multidimensional disease-specific instrument for assessing HRQoL in patients with prostate cancer [6]. In AFFIRM, a responder analysis of HRQoL using FACT-P total score indicated that a significantly higher proportion of patients randomized to enzalutamide had improvements in overall HRQoL compared with placebo [5]. Recent industry guidance [2] encourages the use of cumulative distribution function (CDF) plots, which present the percentage of responders at each score change value, as a supplementary methodological approach to HRQoL responder analyses. CDF plots allow an at-a-glance view of the difference between treatment groups across all possible score changes, rather than at a single score as in a responder analysis.

In this paper, we present CDF plots of the FACT-P data from the AFFIRM study. In addition, we report the longitudinal FACT-P data over 25 weeks of treatment with enzalutamide and placebo in the AFFIRM study population, which include details on domain-specific HRQoL by disaggregating the total FACT-P score.

methods

study design

AFFIRM was a phase III, randomized, double-blind, placebo-controlled study involving 156 sites in 15 countries in Europe, North America, South America, Australia, and South Africa (NCT00974311). The study design details are reported elsewhere [4]. The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Patients provided written informed consent before study participation.

patients

Eligible patients were men with histologically or cytologically confirmed adenocarcinoma of the prostate and castrate levels of serum testosterone (<50 ng/dl), with ≤2 prior chemotherapy regimens, including ≥1 containing docetaxel. All patients had progressive disease at baseline (≥3 increasing values for prostate-specific antigen, ≥2 new lesions on a bone scan, or soft tissue disease progression defined by Response Evaluation Criteria in Solid Tumors) [7].

randomization and masking

Patients were randomly assigned (2:1 ratio) to receive oral enzalutamide 160 mg once daily or identical placebo capsules. Patients were stratified by baseline Eastern Cooperative Oncology Group (ECOG) performance status score (0–1 versus 2) and mean baseline Brief Pain Inventory-Short Form (BPI-SF) score for question 3 (<4 versus ≥4).

functional assessment of cancer therapy-prostate

HRQoL outcomes were assessed using version 4 of the FACT-P instrument completed before randomization, and at weeks 13, 17, 21, and 25, and every 12 weeks thereafter while the patient remained on the study treatment [6]. FACT-P is a 39-item questionnaire with five subscales: physical wellbeing (PWB), social/family wellbeing (SWB), emotional wellbeing (EWB), functional wellbeing (FWB), and prostate cancer subscale (PCS) [6]. In addition, three indices [trial outcome index (TOI) [8], FACT Advanced Prostate Symptom Index (FAPSI) [9], and PCS pain-related score [8]] have been developed to capture the most relevant questions about physical functioning, prostate cancer symptoms, and pain. FACT-P has several empirically derived score differences that are documented as meaningful, surpassing a value that could be considered a minimally important difference (MID). There is no single or certain MID for all applications; therefore, a range of important differences is generally provided. Ranges of likely important differences applied in the present analyses were: FACT-P total score, 6–10 points [8]; FACT-P general health subscale (FACT-G) total score, 5–7 points [10]; all FACT-P subscales, 2–3 points [8, 11]; TOI, 5–9 points [8]; FAPSI, 2–3 points [8]; and PCS pain-related score, 1–2 points [8].

statistical analysis

All analyses described here were exploratory, as per protocol, and conducted to provide a more detailed and elaborate set of sensitivity analyses around the positive planned analyses [5]. The analyses were conducted in the intent-to-treat FACT-P population, defined as all randomized patients who had complete and evaluable FACT-P questionnaires at baseline and at least one post-baseline visit. An evaluable questionnaire had sufficient items to allow calculation of at least one FACT-P subscale.

To estimate longitudinal changes in FACT-P scores from baseline, the primary analysis was carried out using a mixed effects model for repeated measures (MMRM) [12]. MMRM analysis uses all available data and assumes that any missing observations are missing at random. To address the possibility that missing data were not at random, a second analysis was carried out using a pattern mixture model (PMM) with placebo-based pattern imputation [13, 14]. In both models, the following covariates were included: treatment group; time; baseline ECOG score (0–1 or 2); average baseline pain score (<4 or ≥4 for BPI-SF question 3); fatigue severity at baseline (<7 or ≥7 for Brief Fatigue Inventory question 3); age (<65 or ≥65 years); number of prior chemotherapy regimens (1 or ≥2); and baseline FACT-P value. The primary analysis was the change in FACT-P scores from baseline at week 25. Data were analyzed using SAS 9.2 (SAS Institute, Cary, NC), and $P < 0.05$ was considered nominally statistically significant without multiplicity adjustment. Due to the exploratory nature of the analyses, adjustments for multiple comparisons were not made.

The CDF data were presented as a continuous plot of the numerical change in FACT-P scores from baseline on the horizontal axis, with the cumulative percentage of patients experiencing up to that change on the vertical axis. One curve for each treatment group was plotted for each visit.

results

Overall, 1199 patients were randomly assigned to receive either enzalutamide ($n = 800$) or placebo ($n = 399$). All patients completed at least one item of the FACT-P questionnaire at some time point during the study. Baseline scores and at least one evaluable post-baseline assessment were available for 938 patients (enzalutamide $n = 674$; placebo $n = 264$). These patients constituted the intention-to-treat FACT-P population (CONSORT flowchart in supplementary Figure S1, available at *Annals of Oncology* online). Baseline demographics were well matched between treatment groups [4].

questionnaire completion rates and baseline scores

Adjusted FACT-P completion rates at each time point are shown in supplementary Table S1, available at *Annals of Oncology* online. These completion rates, which relate to patients who remained on study treatment, exceeded 80% in both treatment groups at all time points with one exception (placebo group week 61, 67%). The unadjusted completion rates in the intention-to-treat FACT-P population declined in both groups over time, primarily due to study attrition; these rates

were consistently lower in the placebo group than in the enzalutamide group after week 13 (data not shown).

FACT-P scores at baseline were similar between the two treatment groups (Table 1) and consistent with the mean reference values for patients with advanced prostate cancer [6].

longitudinal models

Overall, 67.2% and 31.8% of patients in the enzalutamide and placebo groups, respectively, had no missing data (supplementary Table S2, available at *Annals of Oncology* online). In patients with missing FACT-P data, most presented with a monotonic missing pattern, i.e. patient missed an evaluation and all subsequent evaluations. Treatment discontinuation was the reason for monotonic missing data in almost all patients, with the primary reason for discontinuation being disease progression [enzalutamide: week 13, 78.0% (64/82); week 17, 77.4% (24/31); week 21, 93.3% (42/45); placebo: week 13, 89.4% (93/104); week 17, 76.5% (26/34); week 21, 94.1% (16/17)]. Additionally, 8.9% (60/674) in the enzalutamide group and 7.6% (20/264) in the placebo group had intermittent missing data, i.e. patient missed an intermediate evaluation but then contributed data at subsequent evaluations.

MMRM analysis

Adjusted mean changes from baseline over time for all FACT-P scores are presented in Figure 1. Compared with the pre-established MIDs, the changes observed for all scores in the enzalutamide group were small or negligible. In contrast, the changes observed in the placebo group were considered clinically meaningful for all scores by week 13 or 17, except for the SWB and EWB domains. After 25 weeks, there was a reduction from baseline in FACT-P total score of 1.52 points in the enzalutamide group compared with a reduction of 13.73 points in the placebo group ($P < 0.001$) (Figure 1 and supplementary Table S3, available at *Annals of Oncology* online). A similar result was evident for all other FACT-P subscales and indices.

Table 1. Mean (SD) FACT-P scores at baseline (ITT FACT-P population)

Scale	Enzalutamide ($n = 674$)	Placebo ($n = 264$)
FACT-P total	108.7 (21.2)	110.6 (20.8)
FACT-G	78.3 (15.4)	79.4 (14.7)
Physical wellbeing	21.3 (5.4)	21.4 (5.4)
Emotional wellbeing	17.4 (4.5)	17.4 (4.4)
Functional wellbeing	17.6 (5.8)	18.4 (5.4)
Social wellbeing	22.0 (4.8)	22.0 (4.7)
Prostate cancer subscale	30.4 (7.5)	31.0 (7.5)
TOI	69.2 (16.3)	71.0 (16.3)
FAPSI	22.0 (5.6)	22.4 (6.0)
PCS pain-related	9.7 (4.5)	9.9 (4.8)

For all FACT-P scales and indices, a higher score indicates better quality of life.

SD, standard deviation; FACT-P, Functional Assessment of Cancer Therapy-Prostate; ITT, intention-to-treat; FACT-G, Functional Assessment of Cancer Therapy-General; TOI, trial outcome index; FAPSI, FACT Advanced Prostate Symptom Index; PCS, prostate cancer subscale.

PMM analysis

The estimated change from baseline over time for all FACT-P scores using PMM analysis with placebo-based pattern imputation were similar to those observed in the MMRM analysis (Figure 1, supplementary Table S4, available at *Annals of Oncology* online). In addition, the reductions in all FACT-P scores were smaller in the enzalutamide group than in the placebo group after 25 weeks.

CDF analysis

CDF plots of changes in FACT-P scores at each visit are shown in Figure 2. The distribution functions favored enzalutamide over placebo for the entire range of response levels for FACT-P total, FACT-G total, PCS, FWB, FAPSI, TOI, and PCS pain-related scores.

discussion

HRQoL is an important consideration in prostate cancer, as patients can remain on treatment for many years and may suffer from cancer-related symptoms such as fatigue, anemia, and bone pain [15]. The first chemotherapeutic agent to be licensed for the treatment of hormone-resistant prostate cancer, mitoxantrone, was approved on the basis of HRQoL benefits, even though it did not improve overall survival [16]. Enzalutamide has been shown to significantly prolong overall survival in men with mCRPC after docetaxel-based chemotherapy, compared with placebo, in the AFFIRM study [4]. This study also included a detailed assessment of patient HRQoL using the disease-specific FACT-P instrument. We present the longitudinal FACT-P data from the AFFIRM study which show that, after 25 weeks of treatment, the changes in FACT-P total score and all subscale scores from baseline are significantly smaller (indicating less HRQoL deterioration) with enzalutamide than placebo. Further, the changes observed with enzalutamide were negligible or small. In contrast, placebo-treated patients showed a marked and steady deterioration in HRQoL. Most scores fell within or below the range indicating likely important deterioration by week 13 or 17. Taken together, these results suggest that, in this study, enzalutamide stabilizes HRQoL in patients with progressive mCRPC who, if left untreated, would experience a rapid and clinically significant HRQoL deterioration.

One of the earliest reports that investigated the impact of treatment on QoL on patients with advanced prostate cancer demonstrated that docetaxel, estramustine, and low-dose hydrocortisone significantly improved FACT-P scores from baseline [17]. In the more recent TAX-327 study in patients with hormone-refractory prostate cancer, the median time to QoL response was similar among the treatment arms (3-weekly docetaxel, docetaxel, or mitoxatrone, all with prednisone) [18]. The more detailed analyses reported here further support the improvements in pain and increased time to HRQoL deterioration observed with enzalutamide compared with placebo

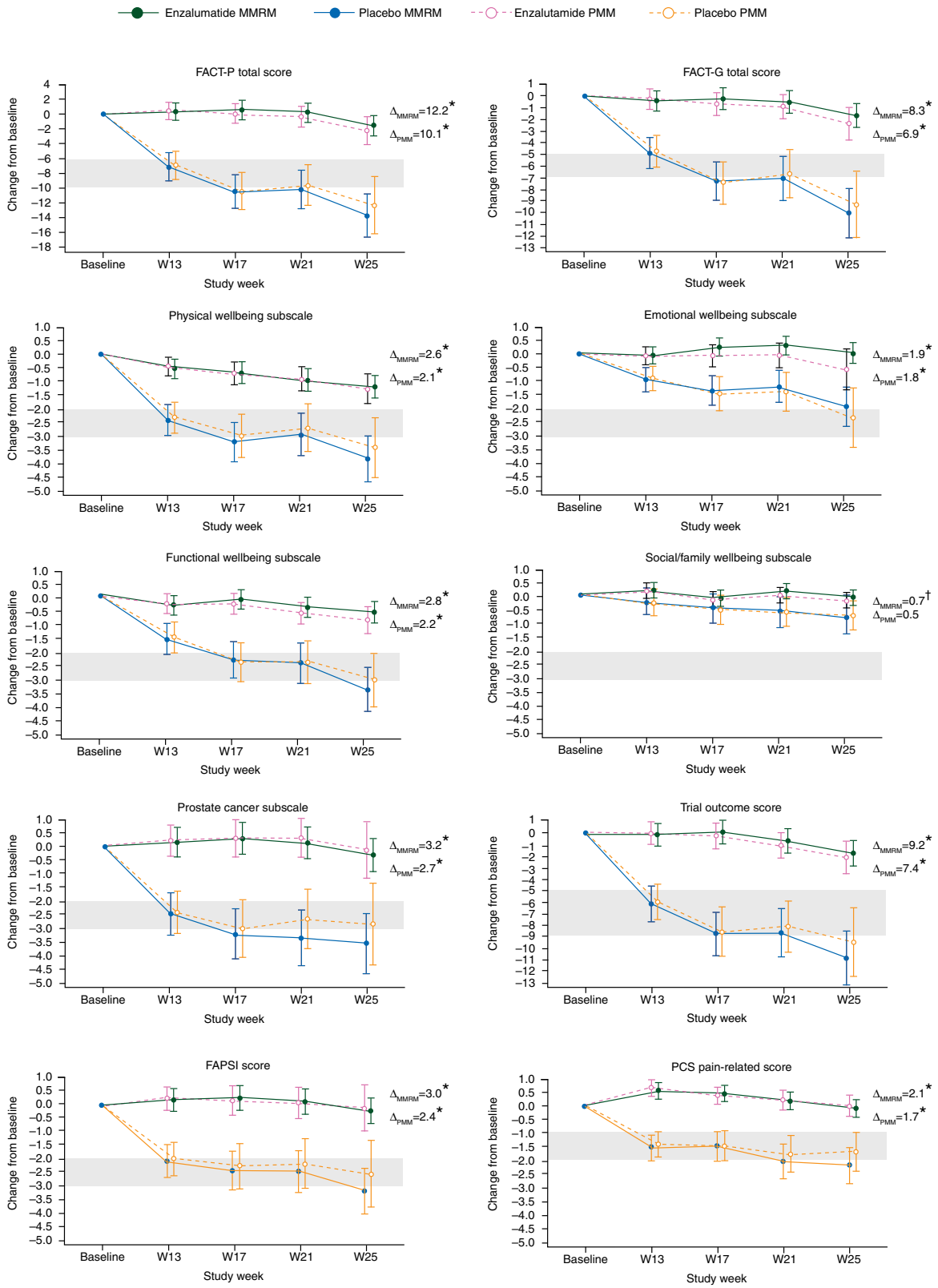

Figure 1. Adjusted mean changes from baseline for enzalutamide and placebo analyzed using MMRM and PMM with placebo-based pattern imputation (ITT FACT-P population). The shaded band on each graph represents the range of likely important differences for each score (see methods for details). Δ_{MMRM}, adjusted mean change from baseline with enzalutamide versus placebo at week 25, MMRM analysis; Δ_{PMM}, adjusted mean change from baseline with enzalutamide versus placebo at week 25, PMM analysis; $^{*}P < 0.001$, $^{\dagger}P < 0.05$. FACT-G, Functional Assessment of Cancer Therapy-General; FACT-P, Functional Assessment of Cancer Therapy-Prostate; FAPSI, FACT Advanced Prostate Symptom Index; ITT, intention-to-treat; MMRM, mixed model repeated measures; PCS, prostate cancer subscale; PMM, pattern mixture model.

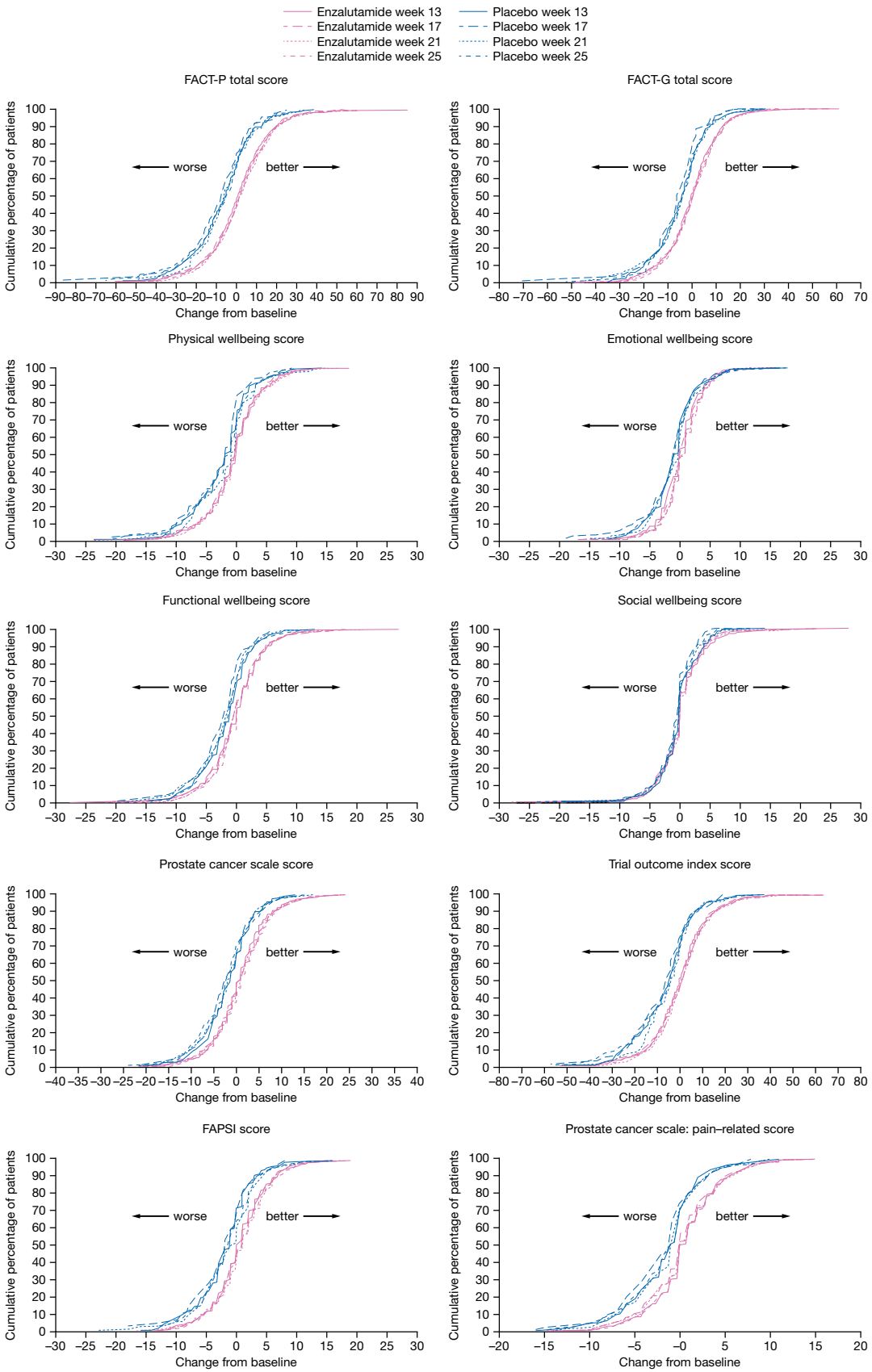

Figure 2. CDF of percent changes of FACT-P scores from baseline for enzalutamide and placebo at each visit (ITT FACT-P population). Note: a positive change indicates improvement. CDF, cumulative distribution function; ITT, intention-to-treat; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-P, Functional Assessment of Cancer Therapy-Prostate; FAPSI, FACT Advanced Prostate Symptom Index.

reported with the BPI-SF and FACT-P in AFFIRM [5]. Similar results on improving HRQoL and delaying HRQoL deterioration assessed using FACT-P have also been reported for abiraterone plus prednisone compared with prednisone alone in patients with mCRPC post-docetaxel [19].

The previously reported AFFIRM prespecified HRQoL responder analysis [5] showed a statistically significant higher proportion of enzalutamide- versus placebo-treated patients had improved HRQoL based on FACT-P total and subscale scores, using a responder definition, i.e. 'a score change in a measure experienced by an individual patient over a predetermined time period that has been demonstrated in the target population to have a significant treatment benefit' [2]. An alternative method of presentation recently advocated by the US Food and Drug Administration [2] is to present the entire distribution of responses for each treatment, thereby avoiding the need to select a single responder definition. CDF plots of the AFFIRM data show clear separation of the curves favoring enzalutamide for all FACT-P scores and subscales, except for EWB, PWB, and SWB. This reinforces the findings from the responder analysis, and suggests that the HRQoL effects of enzalutamide are most marked for the disease-specific and symptom-focused indices, rather than the more general items which would not necessarily be expected to be influenced by drug treatment.

Although various statistical methods (e.g. MMRM, PMM, selection models, etc.) are available to analyze longitudinal data, there is no universally accepted method for handling missing data as each method requires assumptions to be made about the nature of the missing values. A primary analysis alone is not sufficient when there are substantial, non-random missing data. In the AFFIRM study, most patients (~80–90%) discontinued treatment because of disease progression. For the primary analysis, we used MMRM, which assumes that the missing data follow the pattern of patients who remained on study. For the sensitivity analysis, we applied a PMM model with placebo-based pattern imputation, which considers that data may not be missing at random. Placebo-based pattern imputation assumes that, after treatment discontinuation, patients who withdraw from enzalutamide will tend to show outcomes closer to placebo-treated patients. As similar results were observed using both analytical methods (Figure 1), we suggest that the longitudinal findings were not strongly dependent on the nature of the missing data.

While most patients completed the FACT-P questionnaire at baseline, the completion rates decreased at later time points due to attrition associated with disease progression, particularly in the placebo group. This pattern of attrition makes interpretation of data difficult and can lead to overestimation of HRQoL at later time points. To address this imbalance, the MMRM analysis of longitudinal data was limited to 25 weeks. It has also been shown that MMRM works well when there is unbalanced withdrawal [20, 21]. Therefore, the results of the MMRM analysis should be interpreted in the context of a conservative statistical approach, also confirmed by the results of the sensitivity analysis.

A strength of the AFFIRM study was that it involved a large global patient population and the findings are likely to be generalizable to men with progressive mCRPC after chemotherapy. The baseline FACT-P scores of the AFFIRM study population were similar to a reference population with advanced prostate cancer [6] and therefore in line with values that would be expected for these patients. An additional strength of the AFFIRM study was its placebo-controlled design, because, at the time the study was designed, there was no approved second-line therapy following progression on docetaxel-based chemotherapy for patients with castration-resistant prostate cancer.

In conclusion, the survival benefit of enzalutamide is accompanied by stabilization of patient HRQoL, as assessed by FACT-P, compared with placebo in men with progressive castration-resistant prostate cancer after prior docetaxel-based chemotherapy. Application of different analytic methods to the FACT-P data presented here further corroborate the HRQoL benefits observed with enzalutamide in the AFFIRM study.

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disclosures

DC has received consulting fees from Astellas. CI is an employee of Quintiles Consulting, a paid consultant to Astellas Scientific and Medical Affairs and Medivation Inc. in connection with the study design and data analysis for this study. SH, CNB, and JS are employees of Astellas. KF has received fees as an advisory board member for Astellas, Amgen, Janssen, Sanofi-Aventis, Bayer, Orion, Ipsen, Takeda, and Dendreon.

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Differences among young adults, adults and elderly chronic myeloid leukemia patients

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Background: The incidence of chronic myeloid leukemia (CML) increases with age, but it is unclear how the characteristics of the disease vary with age. In children, where CML is very rare, it presents with more aggressive features, including huge splenomegaly, higher cell count and higher blast cell percentage.

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