Repeated measures analysis of patient-reported outcomes in prostate cancer after abiraterone acetate

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Background Metastatic castration-resistant prostate cancer (mCRPC) is typically associated with declining health-related quality of life (HR-QoL).
Objective To assess patient experience with abiraterone acetate (hereafter abiraterone) plus prednisone longitudinally.
Methods COU-AA-302 was a phase 3, multinational, randomized, double-blind study that enrolled asymptomatic or mildly symptomatic, chemotherapy-naïve patients with mCRPC. Patients were randomized to 1 g abiraterone daily plus 5 mg prednisone BID (n = 546) or placebo plus prednisone (n = 542) in continuous 28-day cycles. Patient-reported outcomes (PROs) were collected using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, consisting of 4 well-being subscales (physical, social/family, emotional, functional) and a prostate cancer–specific subscale (PCS). The trial outcome index (TOI) is a composite of the physical well-being, functional well-being, and PCS scores. Least squares mean change from baseline at each cycle up to 1 year (cycle13) was compared between treatment arms using a mixed-effects model for repeated measures, which assumed that data were "missing at random." A pattern-mixture model (PMM) with multiple imputation was performed to address the assumption that data were "missing not at random."
Results Significant differences favoring abiraterone-prednisone were observed for FACT-P total, TOI, and PCS scores, and for all well-being subscales except social/family well-being over the first year of treatment. These results were supported by the PMM with multiple imputation.
Limitations Attrition after 1 year limited our ability to analyze the PRO data beyond that time point.
Conclusions Abiraterone-prednisone confers sustained HR-QoL benefits over the course of treatment.
Funding Janssen Research & Development

Most patients with advanced prostate cancer progress to castration-resistant disease following an initial response to hormonal therapy, and these patients have a much poorer prognosis than those with hormone-dependent prostate cancer.[1,2] Many patients with metastatic castration-resistant prostate cancer (mCRPC) experience rapid health-related quality of life (HR-QoL) deterioration due to complications of metastases and treatment-related toxicities.[3-5] Understanding the benefit of a treatment from the patients' perspective has become an important objective in clinical trials.[6]

The COU-AA-302 trial was a phase 3, multinational, randomized, double-blind study that enrolled asymptomatic or mildly symptomatic, chemotherapy-naïve patients with progressive mCRPC (clinicaltrials.gov: NCT00887x198).[6-8] Using data from the second interim analysis of the COU-AA-302 trial (median follow-up, 22 months; 333 deaths) we previously demonstrated that abiraterone acetate (hereafter abiraterone) plus prednisone significantly delays median time to HR-QoL deterioration (12.7 months vs 8.3 months; hazard ratio [HR], 0.78 (95% confidence interval [CI], 0.66-0.92); P = .003) in patients with chemotherapy-naïve mCRPC compared with placebo plus prednisone (hereafter prednisone alone) as assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score.[9] These findings were confirmed using data from the third interim analysis of the COU-AA-302 trial (median follow-up, 27.1 months; 434 deaths) in which median time to

Accepted for publication February 3, 2016. Correspondence: David Cella, PhD; d-cella@northwestern.edu. Disclosures: Dr Cella is president of FACIT.org and a consultant to Janssen Research & Development, as well as Abbvie, Astellas, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Evidera, GlaxoSmithKline, Helsinn, Ipsen, and Novartis. He did not receive compensation for his effort preparing this manuscript. Drs S Li, T Li, Kheoh, and Todd are employees of Janssen Research & Development. JCSO 2016;14:148-154. doi: 10.12788/jcso.0246.

HR-QoL deterioration (FACT-P total score) was also 12.7 months in the abiraterone plus prednisone (abiraterone-prednisone) arm and 8.3 months in the prednisone-alone arm (HR, 0.79 [95% CI, 0.67-0.93]).[7]

It is of interest to assess repeated measures of patient-reported outcomes (PROs) because they may provide a relevant picture of a patient's experience with treatment. Patients experiencing deteriorating health because of treatment toxicity or progressive disease are more likely to discontinue treatment. As a result, more PRO data are missing in these patients compared with those who continue study treatment. When that occurs, analyses based on completers only may lead to overestimation of the HR-QoL over time. It may also affect group comparisons when rates of dropout or reasons for dropout differ by treatment arm.[8]

To assess patient experience with abiraterone-prednisone longitudinally and to address the challenges associated with missing PRO data, we present a preplanned mixed-effects model for repeated measures (MMRM) analysis and a post hoc pattern-mixture model (PMM) with multiple imputation using data from the first year of treatment in the COU-AA-302 trial.

Methods

Study design

The COU-AA-302 trial enrolled asymptomatic (score of 0 or 1 on item 3 of Brief Pain Inventory-Short Form [BPI-SF] questionnaire) or mildly symptomatic (score of 2 or 3 on BPI-SF item 3), chemotherapy-naïve patients with progressive mCRPC. Overall, 1,088 patients were randomly assigned 1:1 to receive either abiraterone acetate 1 g daily plus prednisone 5 mg twice daily (n = 546) or placebo plus prednisone 5 mg twice daily (n = 542) in continuous cycles. A cycle is defined as 28 calendar days. Study design, eligibility criteria, and primary and secondary endpoint results have been reported. Patient-reported HR-QoL was prospectively collected as a pre-specified endpoint.[7,10,11]

The review boards at all participating institutions approved the study, which was conducted according to the principles set forth in the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. All patients provided written informed consent to participate.

HR-QoL assessments

The FACT-P questionnaire is a validated and accepted questionnaire, comprising a general function status scale (FACT-G, consisting of 4 subscales: physical, social/family, emotional, and functional well-being) and a prostate cancer–specific subscale (PCS) that assesses prostate cancer–specific symptoms and concerns. The trial outcome index (TOI) represents a composite of the scores on the physical well-being, functional well-being, and PCS scales.[12,13]

HR-QoL was assessed on the first day of cycles 1, 3, 5, and 7, every third cycle, and at treatment discontinuation using the FACT-P (version 4).

Longitudinal analysis of repeated measures

The MMRM was fitted to each HR-QoL assessment. Least squares mean change from baseline to week 52 (cycle 13) was compared between the abiraterone-prednisone arm and the prednisone-alone arm at each cycle. Data beyond cycle 13 were not considered for this analysis because of the large number of dropouts beyond this time point. An MMRM was used to estimate the mean FACT-P total, PCS, TOI, and general function subscale scores at each treatment cycle over the first 13 cycles as a function of baseline, cycle, treatment, cycle by treatment interaction as fixed effects, and individual subject as a random effect. The MMRM assumes that the missing data were missing at random meaning that the mechanism of the missing data is independent of the unobserved values.

PMM with multiple imputation

A PMM[14] with multiple imputation approach was also used to analyze the FACT-P total, PCS, and TOI as sensitivity analyses. The PMM differs from MMRM in that it does not assume data are missing at random and takes into account factors likely related to the pattern of missingness. Note that missing not at random means that the missingness depends on the unobserved values, and cannot be predicted solely based on the patients' observed data. First, the missing data were imputed in multiple versions using the control-based approach, assuming that dropouts are missing not at random, and followed the same distribution of completers in the prednisone-alone arm. A mixed-effects model was then fitted to the imputed data as if all subjects had completed cycle 13, and the results were pooled. Mean changes from baseline were estimated and compared between treatment arms.

MMRMs and PMMs were developed using SAS Version 9.4 (SAS Institute Inc, Cary, North Carolina, USA). For all analyses, $P < .05$ was set as the criterion for significance. Due to the post hoc nature of this analysis, no adjustment of type I error was made.

Results

Baseline characteristics and PRO scores

Baseline demographic and clinical characteristics, and PRO scores, were well balanced between the abiraterone-prednisone and prednisone-alone treatment arms (Table 1). Baseline FACT-P data were available for 527 patients (97%) in the abiraterone-prednisone arm and 526 (97%) in the prednisone-alone arm. The FACT-P completion rate was 95% or higher for all cycles, among those remaining patients who were expected to provide data. Of note, patients who discontinued treatment for any reason were not expected to provide data, per protocol. The

TABLE 1 Baseline demographic and clinical characteristics, and mean PRO scores

Characteristic	Abiraterone plus prednisone (n = 546)	Prednisone alone (n = 542)
Median age, y (range)	71 (44-95)	70 (44-90)
Gleason score at initial diagnosis, n (%)		
≤7	225/488 (46)	254/508 (50)
≥8	263/488 (54)	254/508 (50)
Median PSA, ng/mL (range)	42.01 (0-3927.4)	37.74 (0.7-6606.4)
Extent of disease, n (%)		
Bone	452/544 (83)	432/542 (80)
Bone only	274/544 (50)	267/542 (49)
Soft tissue or node	267/544 (49)	271/542 (50)
Other	4/544 (1)	7/542 (1)
Median time, initial diagnosis to first dose, y (range)	5.5 (< 1-28.0)	5.1 (< 1-28.0)
PRO measure, mean (SD)[a]		
FACT-P Total	122.1 (17.0)	122.6 (17.7)
PCS	35.1 (6.1)	35.3 (5.9)
TOI	80.8 (12.9)	81.4 (12.7)
FACT-G	87.5 (12.5)	87.7 (13.1)
FWB	21.2 (5.3)	21.5 (5.3)
PWB	25.1 (3.3)	25.2 (2.9)
SFWB	22.8 (4.5)	22.6 (5.3)
EWB	18.5 (3.9)	18.8 (3.8)

EWB, emotional well-being (score range, 0-24); FACT-G, Functional Assessment of Cancer Therapy-General (score range, 0-108); FACT-P, Functional Assessment of Cancer Therapy-Prostate (score range, 0-156) ; FWB, functional well-being (score range, 0-28); PCS, prostate cancer subscale (score range, 0-48); PRO, patient-reported outcome; PSA, prostate-specific antigen; PWB, physical well-being (score range, 0-28); SFWB, social/family well-being (score range, 0-28); TOI, trial outcome index (score range, 0-104)

[a]Higher scores indicate better functional status.

most common reason for missing data was discontinuation due to disease progression. The CONSORT flowchart for the intention-to-treat FACT-P population is shown in Figure 1.

The estimated mean FACT-P total, PCS, and TOI score changes from baseline at cycles 1 through 13 are shown in Figure 2. Better HR-QoL, as measured by the FACT-P and its subscales, was observed for patients treated with abiraterone-prednisone compared with those treated with prednisone alone. Mean change from baseline in FACT-P total score indicated significant improvement in overall HR-QoL in the abiraterone-prednisone arm compared with the prednisone-alone arm at cycles 3, 5, 7, and 10. Prostate cancer–specific HR-QoL, as measured by the PCS, was significantly improved in the abiraterone-prednisone treatment arm at cycles 3, 5, 7, and 10 compared with the prednisone-alone arm. TOI score was better in the abiraterone-prednisone arm for each cycle, with significantly greater mean change from baseline observed at cycles 3, 5, 7, and 10. Significant differences in favor of abiraterone-prednisone were observed at all cycles analyzed for the physical well-being and functional well-being subscales, and at cycles 3, 5, 7, and 10 for the emotional well-being subscale (Figure 2). No significant between-arm differences were observed at any cycle for social/family well-being (Figure 2).

Pattern-mixture modelling with control-based imputation showed a trend consistent with mixed-effect modelling without imputation (Figure 3). Imputed FACT-P total, PCS, and TOI scores for patients who discontinued were consistently lower than the unimputed scores at each cycle. Nevertheless, abiraterone-prednisone was superior to prednisone alone over the entire 1-year period as shown in Figure 3. Table 2 summarizes the PMM estimates of treatment effect, as well as cycle and cycle by treatment interaction.

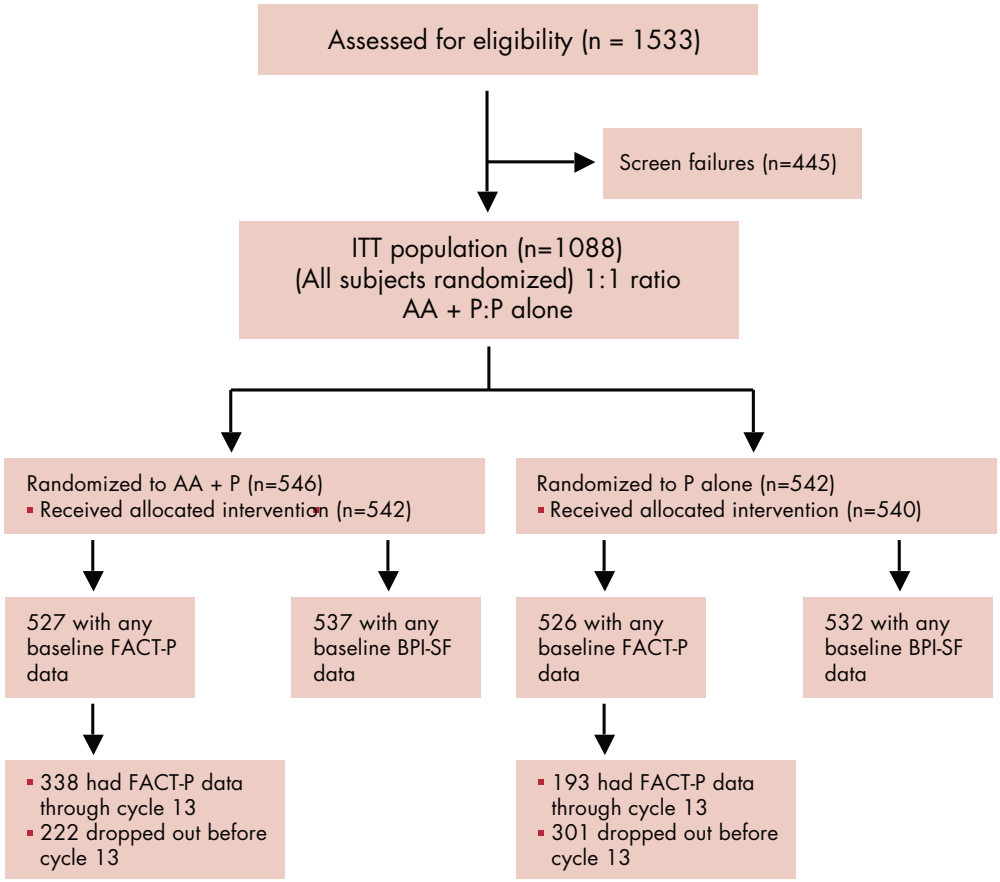

FIGURE 1 CONSORT flowchart of the Functional Assessment of Cancer Therapy-Prostate intent-to-treat population.

Discussion

The results of the MMRM analysis show that FACT-P scores were consistently higher and score changes from baseline significantly favored abiraterone-prednisone compared with prednisone alone, which indicates better quality of life in patients in the abiraterone-prednisone arm. The insignificant between-arm differences at each cycle in the social/family well-being subscale were not surprising as this scale was not expected to be responsive to health status or treatment efficacy. The results of the PMM with multiple imputation were consistent with the findings of the primary MMRM analysis: FACT-P scores were also consistently higher in the abiraterone-prednisone arm compared with the prednisone-alone arm, with a significantly higher mean change in favor of abiraterone-prednisone for FACT-P total, PCS, and TOI.

The clinical meaningfulness of quality of life degradations is defined based on score changes from baseline considered meaningful to patients.[12] In the PREVAIL enzalutamide trial in patients with chemotherapy-naïve mCRPC, a clinically meaningful deterioration in FACT-P total score and subscale scores was observed as expected for placebo-treated patients.[15] However, in our current analysis, no clinically meaningful group deterioration in FACT-P total score and subscale scores was observed at any cycle for the control arm. This is likely because the COU-AA-302 trial, unlike the PREVAIL trial, used prednisone, an active comparator that provided modest benefit to patients. Despite the use of an active comparator in the COU-AA-302 trial, the significant between-arm differences observed throughout the study were consistently in favor of abiraterone-prednisone, suggesting a benefit of abiraterone beyond that observed for prednisone alone.

Figure 3 shows a larger separation of the treatment arms based on the inclusion of imputed data, especially at the later cycles when more patients dropped out. This suggests that the group difference in favor of abiraterone-prednisone observed in the mixed effects model is amplified further by the inclusion of estimates of patient reports after dropout using multiple imputation. As more patients dropped out in the prednisone-alone arm, it seems likely that a larger treatment effect may have been observed if patients had

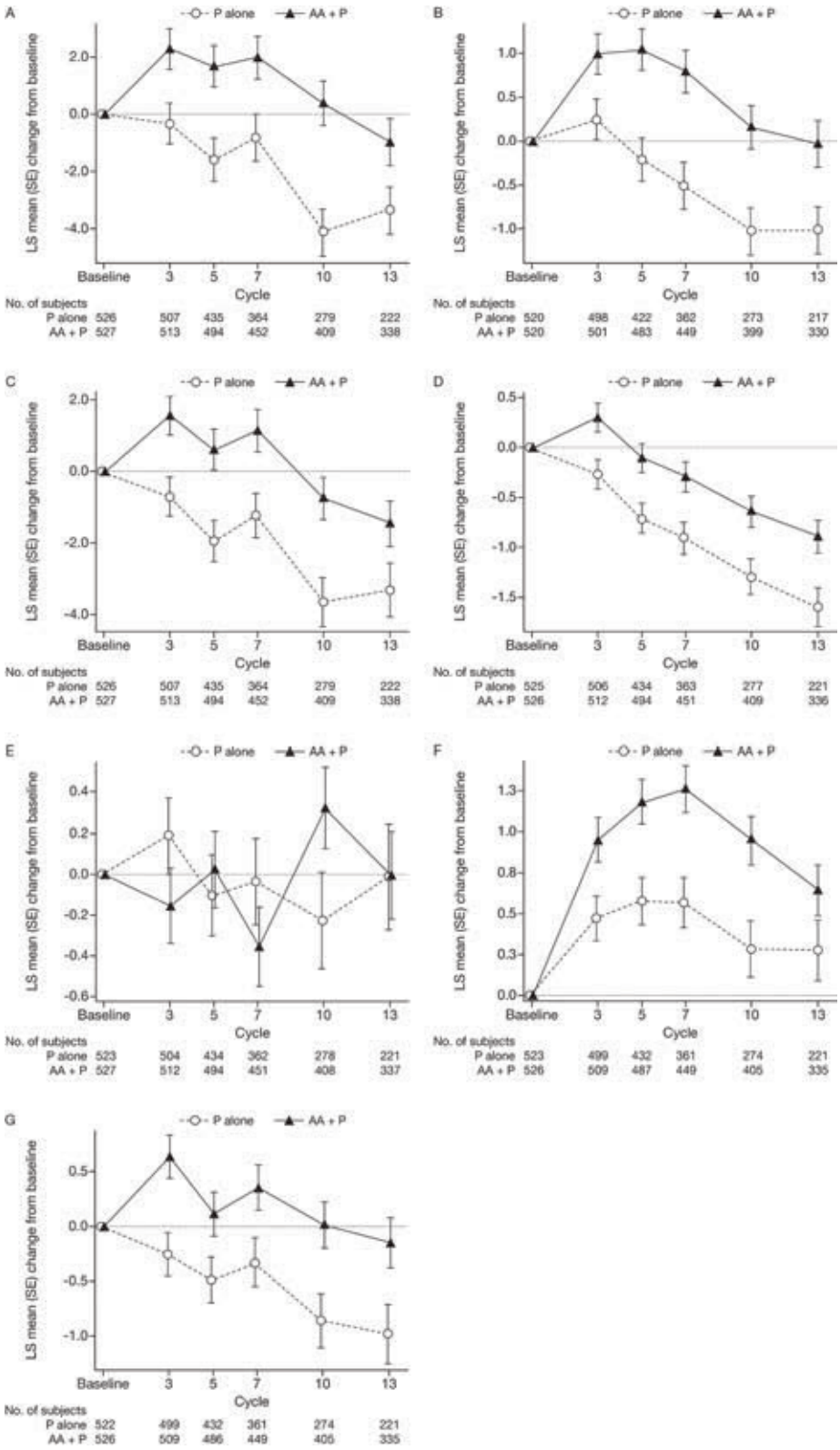

FIGURE 2 Estimated mean change from baseline for patients treated with abiraterone-prednisone or prednisone alone using a mixed-effects model for repeated measures. A, Functional Assessment of Cancer Therapy-Prostate total. B, Prostate Cancer Subscale. C, Trial outcome index. D, Physical well-being. E, Social/family well-being. F, Emotional well-being. G, Functional well-being.

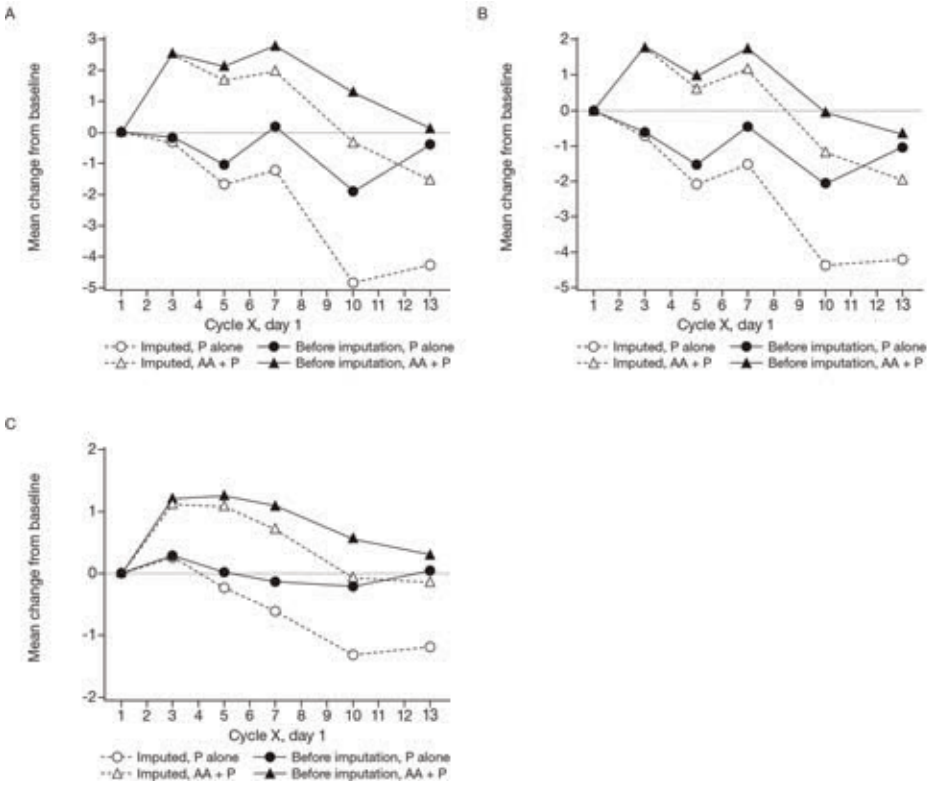

FIGURE 3 Estimated mean change from baseline over time using a pattern-mixture model analysis with multiple imputation. A, Functional Assessment of Cancer Therapy-Prostate total. B, Prostate cancer subscale. C, Trial outcome index.

TABLE 2 Mixed-effects and pattern-mixture model (multiple imputation) analysis of changes from baseline in FACT-P at cycle 13

Parameter	Mixed effects		Pattern mixture (averaged)	
	Estimate	*P* value	Estimate	*P* value
FACT-P Total				
Intercept	1.0823	.1845	0.941	.176
Treatment	2.8019	.0127	3.092	.001
Cycle	-0.4617	<.0001	-0.447	<.001
Treatment × cycle	0.1008	.4482	0.030	.838
PCS				
Intercept	0.7366	.007	0.572	.006
Treatment	0.9757	.0098	1.096	<.001
Cycle	-0.1813	<.0001	-0.156	<.001
Treatment × cycle	0.03817	.3604	0.008	.870
TOI				
Intercept	0.3291	.6068	0.259	.628
Treatment	2.5583	.0037	2.721	<.001
Cycle	-0.3791	<.0001	-0.374	<.001
Treatment × cycle	0.0375	.7251	-0.006	.954

FACT-P, Functional Assessment of Cancer Therapy-Prostate; PCS, prostate cancer subscale; TOI, trial outcome index

continued to report their symptoms and functional status even after treatment discontinuation. Furthermore, trends toward PRO score improvement or decline using available PRO assessments influence future PRO estimates. These findings suggest that it may be useful to collect PROs beyond treatment discontinuation to provide a more complete and unbiased estimate of differences in treatment effects over time, including those patients who discontinue therapy and initiate new treatment.

Although overall survival remains the gold standard for demonstrating clinical benefit in prostate cancer clinical trials, health care providers and payers are becoming increasingly interested in HR-QoL endpoints that reflect the value of treatment to patients.[16,17] The US Food and Drug Administration has provided guidance on the use of validated PRO measures to support labeling claims, noting the substantial clinical benefit of improving how patients feel and function.[18] Furthermore, an extension to the CONSORT statement was recently developed to improve reporting of PRO data, including potential limitations and biases.[19] Although there is no universally accepted method for handling missing data, our analysis overcame some of the bias resulting from missing data by using data up to cycle 13 due to a high number of patient dropouts beyond this point, and using a PMM with multiple imputation approach to support and better inform the conclusions of the MMRM.

In conclusion, the results of our analysis demonstrate that abiraterone-prednisone confers sustained improvements in HR-QoL over the course of treatment. We further show that the superior benefits of abiraterone-prednisone may persist after treatment discontinuation. The use of the MMRM and the PMM with multiple imputation strengthens the previously published time-to-event HR-QoL analyses in these patients.

Acknowledgments

Writing assistance was provided by Lashon Pringle, PhD, of Parexcel and was paid by the funder of the study, Janssen Research & Development. Janssen R&D was involved in the study design, the analysis and interpretation of data, the writing of the report, and the decision to submit the article for publication.

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